

TEXTBOOK OF PHARMACOLOGY

Textbook of Pharmacology

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PREFACE

It is a natural temptation for a teacher to write some books in his subject. Though I had my materials ready for a number of years and had frequently revised them, I had resisted this temptation, knowing fully well how this fascination had detracted several teachers and research workers from the pursuit of active research, which has been a loss to the science.

My second consideration for not writing the book earlier has been based on the fact that teaching materials can more readily undergo yearly changes, whilst a book is re-edited after several years. Though that may not affect the undergraduate students so much, as they are primarily concerned with the basic knowledge in the subject but what is worse still is that a published book from the teacher may make average students complacent and inattentive in the class, forgetting that a good lecture is worth more than any chapter in the book.

Of late, I have somewhat changed these views. Having been actively engaged in teaching and research, for over 3 decades, I know too well how the subject of Pharmacology has become increasingly specialised. Books which were excellent at the time of their first edition in the forties, have during successive edition, become unwieldy and difficult to understand sometimes even by teachers. One may be appreciative of the author's difficulties in getting themselves disentangled from the ever increasing impact of knowledge in the subject, but what about the young students who have to study so many subjects, simultaneously, for passing their examinations? In such a situation, there is likelihood of essentials being missed and non-essentials sticking to the brain of students. An undergraduate is not a specialist. He has to be a basic doctor and learn Pharmacology for knowing the basis of therapeutics. This is possible only if a book ceases to be a compilation but embodies precise, assimilable knowledge of representative drugs, excluding all that is controversial and non-essential for him. This is a hard task involving careful scrutiny and elimination, more than facile acceptances of things from these voluminous research literatures, of today.

It is true that a student has to have some knowledge of a larger group of drugs also, so that during his clinical clerkship, he can follow the teachings in therapeutics, which is now being dominated by special and proprietary drug combinations, widely publicised by manufac-

turers and accepted by clinicians with inadequate scrutiny. To solve this difficulty, the representative drugs of each chapter, have been dealt with in greater detail and the newer ones still under trial, more briefly, at the end, in less prominent prints to convey the meaning of this discrimination, to the students.

Another important point for consideration is the type of book that should be suitable for Indian students, for practising in rural and urban areas, with limited resources for supply of costly drugs. This is a real paradox in our country, today, as the bias of hospital training of students is mostly with newer proprietary drug combinations, vying with each other, for unsubstantiated supremacy over the established ones. Any standard book of Pharmacology has, therefore, to embody essential information pertaining to important drugs, readily understandable and utilisable by average students, without, of course, compromising the scientific aspect of drug knowledge which is *international*. The book thus written should, therefore, be a fairly complete one, combining, knowledge of fundamentals, as well as of applied pharmacology without compromising some of the essential aspects of pharmaceutics and therapeutics, as well.

A student of today is the teacher or practitioner of tomorrow. Like a master artist he should be able to play about with his instruments, *which are drugs*, in this case, in any platform, with ease. He will be an unsuccessful doctor if he does not have basic knowledge of drugs and does not know how to use them for his patients, correctly. His knowledge of Pharmacology, in that case, would be of no avail, in his mission of functioning as a successful clinician. Essential information in respect of important drugs and established therapeutic applications in specified conditions, have therefore been stressed, in each chapter of this book, without going into unnecessary details of any controversial nature.

These objectives, it is feared, are not fully realised by the majority of the existing text books, which, besides being expensive, are either too voluminous and of reference types, or too short and incomplete. There is, therefore, scope for a book, suitable for our conditions, in which, basic scientific principles of fundamental pharmacology, with essential knowledge of pharmaceutics, is embodied. These objectives, it is hoped, have not been missed in the present publication.

The subject of Pharmacology, in the medical curriculum, is taught, along with other para-clinical subjects, on completion of pre-clinical

studies of Anatomy, Physiology and Biochemistry. The students, therefore, are still ill-equipped in their knowledge of clinical subjects. Every effort has therefore been made to make the transition between the two groups of subject as smooth as possible. For this, all important chapters have been introduced with some physio-anatomical background, followed by a brief discussion on the source, preparation, dosage-schedule, metabolism, action, toxicity and finally uses of those drugs that really count, and their relative merits in specified conditions, at the end of important chapters, under the heading *therapeutic considerations*, giving some elementary ideas about the disease processes, for which they are used. To what extent, these efforts have been successful, will be judged by the readers, who alone would know whether a synthesis of this sort in a moderate-sized volume, has been possible.

Whatever may it be, with increasing impacts of scientific knowledge, in every field and expanding scopes of study in the present day medical curriculum, there is need for a book of this type, concise and factual, containing knowledgeable materials, for easy reading and grasping by students, for their examination. Knowing fully well, the problems of present-day students, it is felt that this modest enterprise may be able to fill up the gap to a certain measure and make them understand the essentials of Pharmaco-therapeutics from a single volume for their undergraduate and future post-graduate studies, for which, the book is primarily intended.

As stated earlier, the idea of bringing out this book was taken up late. Though the manuscript was nearly ready for some time, from the materials collected during all these years, the text had to be carefully revised and the illustrations collected and prepared. The task became more strenuous because I had decided about limiting the volume within 850-900 pages which obviously involved more careful selection and presentation of the text materials. Further, due to my impending retirement, the normal facilities at my disposal earlier, for writing a book of this type, under optimal conditions, with the exception of my own undivided attention, became somewhat restricted. This I did not so much grudge, as I have always been of the opinion that a basic text book, meant for undergraduates and the first reading of all post-graduate students, should preferably be either of a *single author* or the team work of his school for maintaining the same trend of thoughts, throughout. The present trend of non-homogeneous multi-author

books is more welcome and suitable for reference books of teachers and students.

When the text was ready, my old and esteemed friend Dr. B. B. Roy of R. G. Kar Medical College, Calcutta, offered his help for going through the manuscript and present it to Messrs. Scientific Book Agency, the well-known publishers of Calcutta, for publication. My thanks are due to both of them for their valuable help towards the final publication of this book, though not without some delay, as is so inevitable, these days.

I am also thankful to my team of colleagues Drs. A. Q. Saifi, R. Vijayvargiya, J. N. Bhatnagar, A. W. Bhagwat, D. Bose, Ratna Bose, V. S. Murthy and H. C. Tripathi, who have so readily helped me in the compilation of the manuscript, preparation of graphs, formulae and selection and preparation of photographs. If the book is found useful, much of the credit will go to them, as they have been closer to the students and more conversant with their points of view. If there is any drawback, which, of course, will be there, that has been due to the shortage of time.

I shall be failing in my duty if I do not convey my sense of gratitude to the Indian Council of Medical Research, for offering me the facilities for scientific and academic activities, on my retirement, as Emeritus Medical Scientist, which have helped me in carrying out the final part of the publication work, in recent years.

This undertaking could not have been completed if the willing co-operation of Mrs. Suman Atrey, Asstt. Librarian, Mr. S. M. Kale and Mr. T. R. K. K. Nair, were not so readily available for typing and retyping the text, during the process of its preparation, and also the help of the College Photographer and Artists—Messrs V. K. Puntambekar, C. R. Wankar and G. K. Berve, who had taken up the work almost as their own, sparing no pains in doing their part of work, within a short time. My thanks are also due to several others, who had associated themselves with the expeditious completion of this work.

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SECTION

I

GENERAL PHARMACOLOGY

CHAPTER

1

SCIENCE OF PHARMACOLOGY

(EVOLUTION, RELATION AND SCOPE)

[Man's inquisitiveness for understanding the mysteries of nature, from which science and medicine have developed, must have been as old as life itself on the planet. It is believed that the hominids or the first race of 'ape-man' might have lived about 10⁶, the second race about 10⁵ and the third race about 50,000 B.C. The concepts of 'Gods' and 'Demons' might have appeared in the neolithic period only. The primitive man hurt by an 'external foe' dealt with him physically. When afflicted by an illness, he took it to be the mischief of an 'internal foe' or 'demon' whom he tried to get rid of by placation or trephining. The mother found her baby unwell and applied a cold sponge for its relief. These thus were the starting points of medical, surgical and nursing cares in the prehistoric days. It was much later, that, when in search of food, he found out poisonous plants and used them against diseases and foes.]

The earliest records of medical practice are traceable in Sumarian, Persian, Egyptian, Chinese and Indian systems. Though some of them had attained a good stature in medical, surgical and Public Health measures, modern medicine started from the Greco-Roman School with Hippocrates, Dioscorides and Galen, between 4th century B.C. to 2nd century A.D. Then followed a long period of over 1,000 years of 'Middle' or 'dark age' during which, the dogmatic teachings of Galen along with 'Arab alchemy', prevailed. Renaissance in medicine, started with Paracelsus in the 15th century A.D., followed by methodical studies of anatomy, physiology, mathematics, physics and chemistry. Nevertheless, progress was still very slow in the 17th and 18th centuries and scientific advances in medicine, started mostly in the 19th century, by which time, pure and basic medical sciences had sufficiently advanced.

Pharmacology like biochemistry, needed the prior development of chemistry and physiology for its scientific advancement. From the beginning of the last century, plant constituents were isolated and studied by animal experimentations with the help of gradually developed physiological techniques and instruments. The work was further facilitated by the discovery of hypodermic needle in the middle of the last century. The initial works of Magendie, Claude Bernard, Ludwig, Buchheim, Schmiedberg, Abel, Dixon and Cushny are of special significance in establishing the science of pharmacology on the sound footing. Towards the latter part of the last and the first half of the present century, with remarkable advances in biochemistry, drug synthesis, microbiology, knowledge of vitamins and hormones, it became

possible to understand the quantitative and cellular nature of drug action, which gradually led to the introduction of chemo and specific therapies, which are now eclipsing all other methods of treatment of diseases in the present era.

The subject of pharmacology comprises of pharmacognosy, pharmaceutics, pharmacodynamics, toxicology, bioassay and therapeutics. It is interrelated with botany, chemistry, physiology and biochemistry on the one hand and with pathology, microbiology, medicine and therapeutics on the other. Its scope has much increased during the last fifty years and it is being oriented more towards specific therapies, in all directions, including systemic, infective, malignancy, immunosuppressive, genetic and fertility problems, with more or less selective actions.]

Use of drugs is as old as diseases. In the earlier days, mostly herbal and chemical drugs were in empirical use and the subject providing relevant information about these drugs was known as *materia medica*. At a later stage, due to the advancement of basic sciences, knowledge of diseases and of experimental techniques, scientific study of drug action was possible. Since then the subject is known as *pharmacology* or the science of drugs.

Due to the advancement of physiology, biochemistry and allied disciplines, this new branch of medicine has developed beyond all proportions during the last one century, so much so that at present, not only drug action in many cases has been established on scientific and quantitative basis but their sites of action, metabolism actions at cellular or enzymatic levels, intricate mechanisms subscribing to the specificity of action as in the cases of chemotherapeutic, antibiotic, vitamins, hormones and other specific drugs have also been determined.

In the light of all these advances, it is now possible to consider and study the subject under the following aspects :

- (1) General pharmacology,
- (2) Special pharmacology,
- (3) Systemic pharmacology.

EVOLUTION

The history of pharmacology is intimately connected up with that of medicine. Struggle for health, struggle against illnesses and struggle for immortality have always been the fanciful dreams of human minds. History of medicine and drugs is thus traceable through different periods of growth of civilization, viz. (a) prehistoric era, (b) earlier periods, (c) middle ages, (d) renaissance, (e) medicine and pharmacology of modern times.

Prehistoric Medicine : Since our life on this planet, there have been illnesses and death and also search for remedies. For a long time, causation of diseases was attributed to influences of supernatural forces with associated efforts for protecting the patients from these demoniacal forces by the use of all sorts of placations and bizzare remedies.

The primitive man, in search of foodstuffs, became familiar with the poisonous nature of certain plants and learned to avoid them and later use them as weapons. The excavations of Sumeria, Mohenjodaro, Harappa and Umr and the paleontological studies of materials, thus discovered, reveal the prevailing knowledge in medical sciences, including surgery and public health in those earlier days.

Earlier Periods : At the dawn of history (3500 B.C.), China, Egypt, Iran and India were the seats of earlier civilization. The development of different schools of medicine is, therefore, seen earlier in those ancient countries.

Iranian, Egyptian and Chinese Medicines : These are some of the earliest recorded systems of medicine, virtually under the monopoly of priests. Some of the contributions of these schools are still in use in modern medicine. Records of Egyptian medicine were maintained in Eber's *Papyrus* from which it is evident that along with the practice of magical amulets, the actual healing art had gradually developed but the administration of medicines used to be preceded by musical recitals. Many prescriptions containing oils, yeast, opium and honey were in use. In the Chinese system of medicine, besides the practice of *acupuncture* or treatment of diseases by needling of skin in different areas, the doctrine of 5 elements—*earth, fire, water, air and metal*, was also conceived. The cause of a disease was thought to lie in an imbalance of these elements. Further, the *doctrine of signature* and use of yellow flowers for the treatment of jaundice, kidney-shaped seeds for kidney diseases and pears for uterine disorders, also prevailed. This gradually developed into what is known as '*Organotherapy*' in latter days. Similarly, for many diseases, musk, elephant and tiger bones, horns, toad's eyes were used. Embalming of dead bodies, use of purgatives, ointments, syrups and poultices are some of the important contributions of these earlier periods.

Ayurvedic Medicine literally means the science of longevity and positive health and is one of the oldest forms of systematised medicine and therapeutics, with theories about diseases, which developed between 2500—600 B.C. in the epoch of *Upavedas*. The important

features in *Nidan* and other treatises of Ayurvedic medicine are as follows :

- (a) *Theory of Tridosha* referring to the imbalance in 'vayu', 'pitta' and 'kapha', causing various disorders, which are reflected on the radial pulse and the diagnosis of diseases made therefrom. This is known as the '*science of pulse*'.
- (b) Monumental work, for those days, in medicine and surgery, as embodied in *Susruta* and *Charak*, compiled about 1000 B.C., the former dealing with surgery and the latter with internal medicine.
- (c) A beautiful *Materia Medica* embodying '*Dravyaguna*' and descriptions of 107 medicinal plants and inorganic chemicals.
- (d) Knowledge of hygiene and public health, as contained in *Manu Sanghita*.
- (e) Use of '*Sammohini*' as an anaesthetic in the Buddhist period.
- (f) Description of tuberculosis, infectious diseases, malaria, leprosy and practice of couching and trephining operations are found in these records.

This ancient medicine, however progressive in those days, could not be claimed to be scientific. Any attempt to integrate it with modern medicine would, therefore, fail as the basic concepts are not scientifically tenable. It is true that some amount of scientific researches on the chemico-pharmaco-therapeutic values of some of these ancient drugs could be carried out but in the light of experience already gained, it is for consideration whether this study should have the priority, as is being given to it in our country at present.

Greco-Roman School: This laid the real foundation of modern scientific medicine, *Aesculapius* (1143 B.C.), known as the son of *Appollo*, and his daughter, *Hygeia*, can be considered to be the earliest recorded figures. He was so famous in his time that he, it is alleged was slain by *Zeus* with the apprehension that he might render all men immortal. To him, we owe the knowledge of the tonic properties of iron and the '*medical emblem*' of the '*Snake and the Wand*'.

Hippocrates (460-400 B.C.) is the father of modern medicine. Before him, medicine was a curious blend of mystic philosophy and predestined observations. It was the genius of Hippocrates to make it rational, ethical and an objective study. His contributions pervaded practically all aspects of medical science, public health and medical ethics. Diseases like tuberculosis, tetanus, epilepsy, hysteria and many others were masterly described by him and similarly, a large number

Plate I

SOME EARLY PIONEERS



FIG. 1. *Aesculapius* (1143 B.C.). A mythical figure ; son of Apollo and endowed with the secret of immortality. The medical emblem, 'Snake and Wand' comes from him.



FIG. 3. *Dioscorides* (A.D.56)
Author of *De Universa Medicina* and the first to systematise knowledge of 800 medicinal plants.



FIG. 2. *Hippocrates* (360—400 B.C.). Undoubted founder of modern medicine, who advocated objective study and left sermons and hippocratic collections behind him.



FIG. 4. *Galen* (130—200 A.D.). A supreme authority, whose doctrine and dogma remained unchallenged upto the 15th century. His polypharmacy and galenical preparations are still known.



FIG. 5. *Paracelsus* (1493—1541 A.D.). Rightly named as 'Luther of Medicine', who strongly decried Galen's dogmatic teachings, spared Hippocrates and advocated chemical study of diseases and medicines. He brought renaissance in medicine.

of drugs—opium, hyoscyamus, scilla and cantharis, to cite a few only, were studied and used. His method of treatment was simple—‘*vis medicatrix*’ or nature cure advocating the value of pure air, dietetic treatment, use of simple purgatives and cholagogues or drugs increasing excretion of bile. Hippocrates was also a saintly man and his ethical rules for the profession embodied in the *Sermons of Hippocrates*, are ostentatiously followed even today. More than 100 books, collectively known as *Hippocratic Collections* or *Corpus* were written by him or probably by his school. His school, however, was weak in theory, but strong advocates of observations, which was partially responsible for bringing the dogmatic Roman School of Galen at a later stage. It may be noted that Aristotle (384-322 B.C.) applied Hippocratic methods of observations in his study of general sciences.

School of Alexandria: With Herophili, as its central figure, it initiated some anatomical studies during this period. *Dioscorides* (A.D. 56) who belonged to the Roman School of Medicine contributed a good deal in therapeutics. He compiled the first extensive *Materia Medica* and described individual crude drugs—vegetable, animal and minerals used in medicine, in alphabetical orders. He also described their methods of preparation, administration and therapeutic values.

In his monumental work *De Universa Medicina*, he incorporated about 800 vegetable and 90 mineral remedies: (a) aromatic plants, (b) organotherapeutic remedies, (c) aloes and scammony as purgatives, (d) male fern for worms, (e) sulphur in pulmonary disease, and (f) castor oil as purgative. He had travelled extensively with the army of Nero and collected newer drugs from other countries, which he systematically arranged and described. The *Doctrine of Signature*, i.e. one medicine for one disease, which had further developed during this period, could be considered to be the starting point of pharmacognosy or identification of drugs of today.

Galen (A.D. 130-200) belonged to the Roman School of Medicine and was considered to be the supreme authority in medicine and pharmacy for nearly 15 centuries. He was the last scholar of the Alexandrian School and undoubtedly the most prominent figure after Hippocrates. Though his name in Greek meant calm, he was a man of great dynamism and drive and also vain and sophisticated. Unlike Hippocratic teachings which stressed observations and not theories, Galen's teachings were rich in theories and dogmas and had thus an initial appeal to the profession.

(a) His contributions in anatomy, from the dissection of monkeys and pigs, sustained for 12 centuries upto the time of *Andreas Vesalius*.

(b) His contribution in physiology, based on *vivi section* and other studies which laid the foundations of experimental physiology, prevailed upto the time of *Harvey* in the 17th century.

(c) His contributions in pharmacology were by far the maximum. He outlined elaborate principles of drug action and gave combinations of drugs according to their elementary qualities of heat, cold, moisture and dryness for making them more effective in different diseases. This is known as the *Polypharmacy of Galen*, which later on, led to the introduction of *Theriacque*, consisting of 60 drugs and considered to be a panacea for all diseases. It dominated the therapeutics of middle ages and was removed from French Codex only in 1908. Galen wrote about 30 books in medicine, including *materia medica* and was a voracious reader and writer of his time. The authority of Galen, rightly or wrongly, remained unassailable till the period of Reforms after Renaissance. To Galen, we owe the name of *galenicals* in pharmaceutics, which are spirituous crude preparations and extracts of medicinal plants. The astringents, emollients, anodynes, elixirs, antidotes, tinctures and extracts were introduced in therapeutics, for the first time by him.

Middle Ages (A.D. 600-1400) : During this period which witnessed the spread of Christianity and also the rise of Islam, there was further progress in pharmacology mainly due to the development of *Arabic Alchemy*.

Although initially, the Arabs continued the traditions of Greece and Rome, but soon they developed a vital interest in drugs, as they controlled the trade of spices and drugs through the Red Sea. *Rhazes* and *Avicenna* were the important contributors to Arabic Alchemy. The important work of the latter, known under the name of *Canon*, was followed in Europe almost upto the middle of the 17th century.

Preparations of plant medicines by the pharmaceutical processes of *sublimation*, *elution*, *coagulation* and *calcination* were introduced by this school. Drugs like manna, senna, cassia, rhubarb, tamarind and also syrup, elixir, absorbent cotton, musk, camphor, crude anaesthetics, and metallic preparations were brought into use and opium continued in popular uses as before.

Salerno School (A.D. 1100-1500) : This pursued the traditions of galenical teachings and incessantly searched for another *Theriacque*. The two crying ambitions of this period were production of artificial gold and an elixir of life, both of which of course proved utter failures.

Uses of gold, mercury, arsenic and ammonium salts were made popular by this school.

Renaissance (A.D. 1400-1600) : The unending period of middle or dark ages from the time of the decadence of the Greco-Roman School upto the end of the 14th century, during which stagnation, scholastic dogmatism and hero worship were prevalent, culminated in a type of internal revolt in the minds of men for correct thinking and learning.

This brought about a period of over 200 years, known as Renaissance (rebirth or revival), changing the outlook of philosophy, literature, science and technology. Discovery of printing and navigation also subscribed to this regeneration.

The contributions of *Copernicus*, *Galileo*, *Bacon*, *Descartes*, *Newton*, *Boyle* and many others were particularly significant. Systematic study of botany, refuting the misconceptions of *Pliny* of the 1st century A.D., organisation of museums and botanic gardens, starting of societies like *Royal Society of London* and *French Academy of Paris*, were some of the outcomes.

In anatomy, the work of *Leonardo da Vinci*, and *Andreas Vesalius* and in physiology, the discovery of circulation by *Hurvey* (1575-1657), capillary circulation by *Malpighi* (1628-94) with the microscope discovered by *Leewen Hoeck* (1632-1720), gradually paved the path for modern medicine. .

Most of the manuscripts were printed. A tendency for going back to Hippocratic Medicine, at the exclusion of the teachings of the *Arabic School* as well as of *Galen*, gradually developed. This is known as 'Reform' and *Paracelsus* was the central figure in this revolution.

Paracelsus (1493-1543) : A German by origin and a veritable *Luther of Medicine*, he was bitterly disappointed with the existing conditions of medicine and started a deep study of chemistry. He introduced *chemical pharmacy* in place of *galenicals* and tried to establish chemical theories of diseases, instead of the humoral concepts, prevailing then.

This half mad man was a great revolutionary and was possibly the first of his type, after nearly 1400 years, to challenge the authority of *Galen*. He burnt all his writings in public but spared *Hippocrates*. He was the precursor of *Bacon*.

The *Chemistry of Paracelsus* was very rudimentary but gave an incentive to the study of medicinal chemistry which eventually could bear fruit only in the 19th and 20th centuries, when chemistry

SCIENCE OF PHARMACOLOGY

was appropriately developed. We owe several drugs like antimony, arsenic, sulphur, tincture of gold, to Paracelsus.

The 15th and 16th centuries also found the rise of the *Italian School of Medicine*, known for its anatomical research initiated by Vesalius (1414-1464). Modern anatomy is the outcome of the laborious contributions of this great worker and students from all over Europe used to come to his school for learning anatomy.

Therapeutics during renaissance, however, remained poor. The same old drugs and also turpentine, thymol, clove oil were in use. Bleeding and purgatives continued to remain the important methods of therapeutics. SPA treatment became popular.*

17th Century : The results of renaissance were vividly observed during the 17th century. Wealth of scientific research and discovery, an ardent desire to understand the laws of nature were manifest and experimental nature of science clearly realised. So far as drugs, use of mineral medicines—the triumphant chariot of antimony tartar emetic, the need for chemical research, started producing tangible results.

Outstanding workers of the period were :

- (a) *Willis* in anatomy,
- (b) *Harvey* in physiology,
- (c) *Vanhelmont* and *Sydenham* in clinical medicine.

The *School of Iatromechanic and Iatrochemistry* was born during this period. This had, as concept, the origin of diseases in tone—either relaxation or increase. The line of treatment as advocated by these Schools therefore consisted of :

- (a) Cauterization, scarification, blistering and friction.
- (b) Use of stimulants—tea and coffee—introduced from China and Arabia respectively and considered to be panaceas for all diseases, including dyspepsia, with records of use of 200 cups of tea per day during this period.
- (c) Also the empirical uses and applications of : (i) *Cinchona*, imported from South America and used in malaria, (ii) *Ipecac*, imported from Brazil and used in dysentery, (iii) *Laudanum of Sydenham* for pain, and *Dover's powder* as diaphoretic, (iv) *Iron* in cachexia and melancholia, and (v) *Lime water* as antacid.

Publication of *London Pharmacopoea* was made for the first time in 1618 and drugs like guaiacum, sarsaparilla, tobacco, peru balsam, also came into use. *Baglivi*, the Italian worker, introduced *animal experimentation, and intravenous transfusion* without success.

Plate II

THEY LAID THE FOUNDATION OF SCIENTIFIC ANATOMY, PHYSIOLOGY AND PHARMACOLOGY



FIG. 6. *Andre Vesalius* (1414 — 1464 A.D.). Known for his anatomical research and was the founder of modern anatomy and of the first 'School of Anatomy' in Padua.



FIG. 7. *William Harvey* (1575—1657). An outstanding physiologist who discovered circulation.



FIG. 8. *Friedrich Wilhelm Serturner* (1784—1841 A.D.). The German apothecary who isolated the first alkaloid, morphine, in 1807 and studied its effect on himself.



FIG. 9. *Francois Magendie* (1782—1855 A.D.). The French scientist who was the founder of 'Experimental pharmacology'.

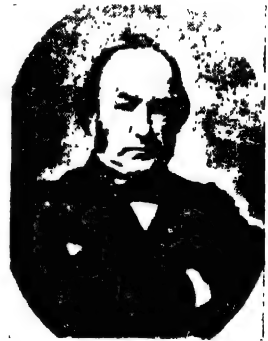


FIG. 10. *Claude Bernard* (1813—1878 A.D.). A pupil of Magendie and founder of 'Experimental Medicine': An outstanding physiologist and pharmacologist who introduced scientific methods in medical research and gave the concepts of 'glycogenic functions' and 'milieu interieur'.

18th Century : If a start in the scientific study of medicine was made in the 16th and 17th centuries, it could produce perceptible results only from this century. It is during this period that we find thinkers and writers like Rousseau, Leibnitz, Kant and Voltaire who considerably influenced the thinking process and orientation of people while Lavoisier, Cavendish, Dalton, Scheele, Priestley and others gave birth to the chemistry of today.

The outstanding figures in medical science during this period were :

- (a) Boerhaave, Hoffman and Broussais in medicine,
- (b) Galvani and Volta in electrophysiology,
- (c) Cullen in materia medica,
- (d) Jenner, the discoverer of smallpox vaccination.

The following drugs also were brought into use during this period :

- (a) Glauber's salt as a purgative,
- (b) antimony as an emetic,
- (c) mercury as antisyphilitic,
- (d) digitalis as diuretic and cardiotonic,
- (e) arsenic in malaria,
- (f) aconite and belladonna in pains and inflammation.
- (g) lead and zinc in skin diseases.

Smallpox was rampant in Europe in those days and in Paris alone, 20,000 people died in a few months from this single disease whereas there is hardly any case anywhere in Europe at present.

It is interesting to note that though knowledge had grown by bits, it was yet hardly rational and still complicated by the *vitalistic theory* of Hoffman. Major devices of therapeutics of this epoch, as advocated by Boerhaave, Sydenham and Gregory, were : (a) Use of *drastic purgatives*, almost unto collapse leading to the popular saying '*Il est mort guéri*'—he is cured by death. (b) Use of *blood letting*—Louis XIV was bled about 300 times in his life. In 1827, 32 millions of leeches were used in France. Hence medicine was nicknamed as *Vampire medicine*.

Voltaire, the great satirist philosopher and thinker, cynically exhorted: "*Medicine is the science of pouring of drugs, of which, one knew little, unto patients, of whom, the doctor knew less.*"

Rise and Fall of Homeopathy : It was against this background that Hahnemann, the *founder of Homeopathy*, revolted and introduced his new system of medicine. He was an eminent doctor of Leipzig who had lost all his family members during an epidemic without possibility

of any redress. He then spent his whole life in his work which is embodied in his writings, *The Science and Art of Homeopathy*, under the name of *Organon* outlining his new theories of diseases and their treatment; and his laborious work on drugs is embodied in *Materia Pura* after studying the action of diluted drugs on healthy human volunteers, including himself, thus permitting compilation of subjective symptoms with comparatively atoxic drugs.

The fundamental principles of Homeopathy are based on the following concepts :

(a) *Similia similibus curantur* or like cures like, e.g. headache is to be cured by a drug which can produce headache on healthy human beings ; and similarly constipation, or any other disorder. This he tried to explain by his vital force theory and is now comparable to the modern concept of 'substrate competition'.

(b) All diseases are due to 'three miasms'—'psora', 'syphilis' and 'sychosis', the first referring to skin diseases and the third to gonorrhoea. In his concept, all diseases make themselves known by exteriorisation from symptoms and drugs also show their effect in a similar manner. A suitable drug for a case could thus be selected by matching the symptom complex which would vary from individual to individual even when the disease might be the same.

(c) '*Dilution*' of a drug—in decimal or centesimal scale (10 or 100 folds), increased its potency. The mother drug diluted to 1 in 100 gave potency 1. This diluted to 1 in 100 gave potency 2. In this way, potencies of 30, 200, 1000, lac and million could be obtained. The increase in potency was ascribed to the subdivision, disintegration and ionic dissociation of drug molecules, by the process of trituration, with a solvent, which concept, of course, is not scientifically tenable.

Hahnemann's 30th potency is equivalent to the concentration of 10^{-60} , i.e. one molecule of drug in the sphere of Neptune, as worked out by Clark. His disciples now readily use 10 million potencies. Where is the drug then? It is almost like putting a drop of drug in the Ganges at Hardwar and drinking the water as medicine in Calcutta.

The doctrines of Hahnemann appear to be sweeping generalisations and not scientifically tenable. Even with our knowledge of ionisation and atomic dissociation, the 'dilution theory' in Homeopathy cannot be explained. Due to the pioneer work of Clark and his associates, it is now established that for producing an action, there must be sufficient number of drug molecules per cell of the body for effecting physical or chemical changes, required for eliciting any response, an obligation not fulfilled by this system.

Plate III

THEY LAID THE FOUNDATION OF ANAESTHESIOLOGY, BACTERIOLOGY AND ANTISEPSIS



FIG. 11. *Horace Wells*. Discovered ether, the first general anaesthetic of real value in surgical operations, in 1846.

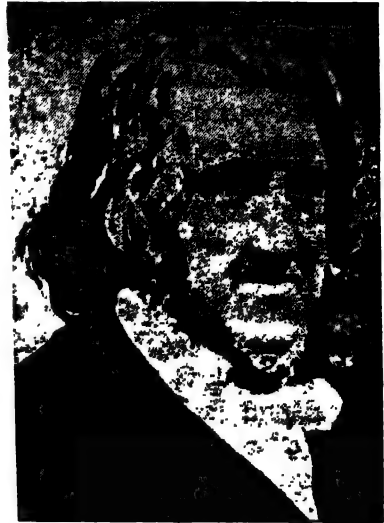


FIG. 12. *James Simpson*. Discovered chloroform in 1847 and ceaselessly combatted ecclesiastical and other oppositions to promote its use in surgery.



FIG. 13. *Louis Pasteur*. The chemist-bacteriologist, whose life-long work established bacteriology firmly and placed him on the pedestal of 'premier microbe hunters',



FIG. 14. *Joseph Lister*. Discoverer of the antiseptic property of phenol. His work along with that of others, established asepsis and antiseptic on a solid foundation, permitting the development of modern surgery.

Homeopathy grew fast all over the world and has almost been completely discontinued as an unscientific system of medicine.

However, of the two systems of medicine of the 18th and early 19th century, homeopathic medicine, if not active, was not harmful to the system as allopathy was, the former allowing the body mechanism to deal with the disease whereas allopathic medicines were capable of hindering the same.

Homeopathy leaves behind a vast lore of information about plant, mineral and biological medicines and it may be worthwhile studying some of them by scientific methods sometimes in future.

Modern Medicine: It has been observed that though scientific advance had been taking place by stages, it was only in the 19th century that an all-round development in various fields of medicine was possible, leading to the development of modern medicine. This was a brilliant period in the annals of medicine and much scientific work was carried out in France, Austria, Germany and England during this period.

The work of *Broussais*, *Courvoisier* and *Laennec* in France, of *Addison* and *Hutchinson* in England and of *Skoda* in Germany laid the foundation stone of diagnostic methods in clinical medicine. The carefully conducted investigations of *Louis* had proved, beyond all doubts, the futility of the prevailing system of therapy with over-drugging and drastic measures, which view on therapeutic nihilism was also readily shared by the *Viennese School of Medicine*.

It was during the last three quarters of the 19th century that *Maggendie* and his pupil, *Claude Bernard*, established the role of experimental medicine, physiology and pharmacology and *Paul Broca* and *Charcot* made their magnificent contributions in anatomy, anthropology and nervous diseases. A little later, the work of *Louis Pasteur* and *Koch* laid the foundation of bacteriology and *Virchow* established the role of cellular pathology.

Discovery of general anaesthetics in the middle of the century by *Wells*, *Simpson* and *Davy* and of carbolic acid as antiseptic by *Lord Lister*, an ambition cherished from the days of *Ambroise Paré* and *Simmel Weise*, completely changed the outlook of surgical interventions towards the latter part of the century.

In this perspective, modern medicine, surgery, pathology and bacteriology were born, anatomy and physiology having already been developed.

EMERGENCE OF PHARMACOLOGY

It has been seen from the foregoing how different branches of medicine had advanced by stages. It was only when basic sciences of physics and chemistry had sufficiently been established, it was possible for physiology and biological sciences to develop. Pharmacology, for obvious reasons, had to develop last, in as much as, for its advancement, not only knowledge of chemistry and physics was required, but also of physiology, biochemistry and bacteriology.

Some of the important milestones for the development of pharmacology are as under :

Isolation of Pure Drugs and Chemicals : Morphia, the first alkaloid, was isolated by *Serturner*, a German apothecary, in 1807 and quinine and strychnine by *Pelletier and Caventou*, the French apothecaries in 1818 and 1820. In rapid succession, other alkaloids—caffeine, emetine, papaverine, cocaine, ephedrine, eserine—were then isolated, permitting the study of all these alkaloids pharmacologically.

In 1783, digitalis was masterly studied by *William Withering* and its cardioactive glycosides isolated and studied by *Schmiedeberg* and others towards the end of the 19th and the beginning of this century. During the same period, a number of antiseptics, anaesthetics, antipyretics and hypnotics like chloral hydrate, urethane, chloralose and paraldehyde were prepared and work on hormones was also initiated.

Drug synthesis : *Louis Cadet*, the French apothecary, had succeeded in attaching arsenic to a carbon atom in 1760 and *Wohler*, the German chemist, synthesised urea for the first time in 1828. Since then many new compounds were synthesised, which ultimately culminated in the discovery of organometallic arsenicals in 1907 by *Paul Ehrlich*, which established for the first time the *School of Chemotherapy*. In this way, drug synthesis gradually started replacing the natural drugs which were hitherto the only available sources for medicine.

Techniques and Appliances : Development of experimental techniques started almost from the days of Harvey, but so far as real advances in techniques and appliances are concerned, they occurred from the days of Magendie, his pupil Claude Bernard and a large number of other pharmacologists of a later period, who established the *School of Experimental Medicine*.

Alexander Wood of Edinburgh invented hypodermic needles in 1853. According to modern advances, this may today appear to be such a simple thing as bicycle also appears to be now but it revolutionised the method of drug administration and advanced the cause of experimental pharmacology beyond imagination.

Plate IV **SOME OF THE EARLIER ARCHITECTS OF** **MODERN PHARMACOLOGY**



FIG. 15. *Rudolph Bucheim* (1820—1875 A.D.). Made his own house into a laboratory for experimental pharmacology. Studied many drugs and chemicals, classified them and tentatively conceived of cellular mechanism of drug action.



FIG. 17. *John J. Abel* (1857—1938 A.D.). A pupil of Schmiedeberg, who made his laboratory in John Hopkins, a pilgrimage for pharmacologists from all over the world.



FIG. 16. *Oswald Schmiedeberg* (1838—1921 A.D.). A master-mind and builder of basic pharmacology. From his school his pupils spread out all over. His contributions on muscarine and other alkaloids, strophanthus, drug metabolism and structure action relationship are outstanding.

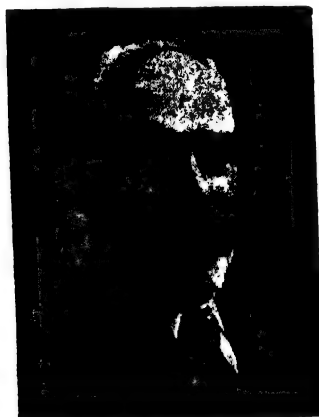


FIG. 18. *A. R. Cushny* (1856—1926 A.D.). Another student of Schmiedeberg and successor of Abel. His contributions on cardiac glycosides, diuretic, techniques and instruments are still considered classical.

Carl Ludwig (1816-95) was the first to invent and use kymograph, writing point and also blood pump for the study of gases. This was a very important step in the study of drug action on experimental animals.

During the last half of the century, many basic techniques—manometry, spectrometry, electrical stimulation of muscle-nerve preparations, cannulation, cardiography and heart-lung techniques—were introduced and in the earlier part of the present century, blood gas analysis, study of conditioned reflexes, isolated organ studies, chromatography, cross-circulation, decerebration and tissue respiration studies were brought into use.

Pharmacological Studies : The pure drugs, thus discovered, were masterly studied by a large group of earlier workers, of whom, the following names deserve special mention as they established fundamental pharmacology and gradually initiated the broad principles leading to the concepts of *modern pharmacology*.

Francoise Magendie (1783-1855), probably the first experimental pharmacologist who started his work in the thirties of the last century was the forerunner of Claude Bernard, Buchheim and Schmiedeberg. He studied the principal alkaloids isolated—emetine, morphine, strychnine, etc. Coffee, alcohol, hydrocyanic acid, ammonium salts and emetics were also studied by him.

Claude Bernard (1813-1878) : Another French scientist of premier order and founder of experimental medicine, who contributed equally to physiology and pharmacology. His discovery of glycogenic function of the liver, concepts of 'milieu interieur', site of action of curare and strychnine, besides studies of other alkaloids and chemical substances, are only a few instances of his contributions to scientific medicine.

Rudolph Buchheim (1820-1879) : A German by origin who established an experimental pharmacology laboratory in his own house and studied almost all the drugs known—chemicals, purgatives, mydriatics and anthelmintics. He attempted a pharmacological classification of drugs and also conceived of cellular mechanism of drug action.

Oswald Schmiedeberg (1838-1921) succeeded Buchheim as professor and is known not only for his outstanding contributions in fundamental pharmacology, but also for creating a *School of Pharmacology* with a galaxy of pupils—*Abel, Cloetta, Cushny, Gottlieb, Jacquet* and many others, who as the first group of disciples, inspired by their training in experimental pharmacology from their great master, carried the torch of their knowledge to their respective countries. Study of nicotine, muscarine, physostigmine, strophanthus, synthesis

of urea from ammonia and of basic concepts of drug metabolism and structure-action relationship are accredited to this pioneer worker.

Binz (1832-1922) is known for his work on quinine, alcohol, arsenic and anaesthetics and his lectures, published in the form of a book by the *Sydenham's Society*, was one of the earlier books in the subject.

Boehm (1844-1926) : A pupil of Ludwig who later succeeded Schmiedeberg. Some of his prominent pupils were Straub, Fuhner, Trendelenberg, all known for their outstanding contributions to techniques, appliances and drug actions.

J. J. Abel (1857-1938) : A student of Magendie, Buchheim, Claude, Bernard and Schmiedeberg, who can rightly be considered to be the "Father of American School of Pharmacologists". He worked at John Hopkins and made his laboratory a veritable Mecca for pilgrimage and work of many others from all over the world. He worked on epinephrine, insulin, sulphobromophenolphthalein, posterior pituitary, antimony preparations and also invented the vivi-diffusion apparatus.

A. R. Cushny (1856-1926) : A successor of Abel, whose masterly work in John Hopkins and later as professor of pharmacology in the Edinburgh University, on primary and secondary actions of digitalis, diuretics, threshold and non-threshold substances remains classical even today. His heart-lung-kidney perfusion and myographic techniques are still in use.

W. E. Dixon (1871-1931) : An eminent pharmacologist and an excellent teacher, experimentalist and writer, who made pharmacology a living subject in Oxford in his time.

Modern Pharmacology : The fundamental work carried out by these earlier pioneers were further detailed by a large number of workers of the present century, referring particularly to the following :

- (a) Localisation of drug action,
- (b) Mode of action of drugs on cell components and enzyme systems,
- (c) Structure action relationship and substrate competition,
- (d) Biological antagonism and role of metabolites and antimetabolites in the mechanism of drug action and drug resistance,
- (e) Local hormones, and
- (f) Bioassay or quantitative pharmacology,
- (g) Concepts of molecular and genetic pharmacology including immunosuppressive, antimalignancy and antifertility agents.

These works have now oriented the subject towards cellular, enzymatic and quantitative pharmacology leading to the discovery of *specific therapies*.

For achieving this latter end, many have been the architects in recent years, each one contributing his best in his own domain, but the names of the following deserve special reckoning :

- (a) Dale, Otto Lowei, Reid Hunt, Cannon, Bach, Von Euler—'autonomic drugs',
- (b) A. J. Clark, Traube, Lechetallier—mode of action of drugs on cells,
- (c) Burn, Trevan, Gaddum, Von Wijngaarden—bioassay and quantitative pharmacology,
- (d) Gaddum, Wood Fildes, Wooley Shaw—metabolites, antimetabolites and substrate competition.

Thus, within a short span of less than a century, much ground has already been covered and the result of this accumulated knowledge has led to the discovery of *challenging drugs* for the conquest of many intractable diseases including infective conditions. The restless search continues till a specific drug for each disease is found out.

PHARMACOLOGY—ITS RELATION AND SCOPE

The term pharmacology is derived from the Greek roots—*pharmakon* meaning drug and *logos*, meaning discourse or knowledge ; in other words, a subject dealing with the knowledge of drugs, the word knowledge referring to didactic and rational knowledge, as opposed to an empirical one. Hence the subject is now known as the science of pharmacology.

The term '*materia medica*' is still sometimes loosely used in place of pharmacology. The former refers to the subject dealing with the description of materials, used for the treatment of diseases, which connotes empirical knowledge. This does not, however, mean that the subject of pharmacology, as prevailing today, possesses nothing but scientific knowledge. Knowledge grows by stages. Being a scientific discipline, pharmacology is trying to understand and unveil drug action by animal experimentation but there are still many drugs, used in therapeutics, for which no scientific basis is yet known.

Branches : The subject of Pharmacology comprises of the following sections :

Pharmacodynamics refers to the study of action of drugs on living organisms. Any action is dynamic and hence this nomenclature. In Section II, Chapter 6, we will have occasion to study how drug action is determined on protozoa, isolated organs, organs in situ of various

laboratory animals and how these actions are finally integrated with a view to obtain a complete picture of the nature and mode of their action. All these come within the purview of this branch of the subject.

Pharmacy and Pharmaceutical Chemistry : Pharmacy is concerned with the preparation, labelling and dispensing of medicinal preparations, according to the prescriptions of the doctors. This refers to the dispensing of mixtures, emulsions, pills, powders, etc. Though this work is entrusted mostly to dispensers, nevertheless, some knowledge of this subject is essential in our country where galenical pharmacy is still prevailing in rural areas. *Pharmaceutical Chemistry* is concerned with the commercial manufacture of official, non-official and proprietary drugs, obtained from crude sources or by synthesis. It is also concerned with drug analysis for determining the purity and strength of pharmaceutical preparations. The subject is beyond the scope of our present study.

Pharmacognosy : This literally means *identification of drugs*. This is done by the study of physical, chemical and biological characters as well as macroscopic and microscopic studies of plants. It is an important branch of study and helps in the identification of authentic drugs by elimination of spurious ones. The subject also takes into cognisance the active principles contained in crude drugs. Good knowledge of botany and chemistry is essential for this work.

Toxicology : This refers to the knowledge of the toxic properties of drugs acting as poisons. Therapeutic uses of a drug refer to the treatment of diseases, whereas toxic action follows criminal or accidental use or after use of a drug even in therapeutic doses.

Criminal toxicology is dealt with in medical jurisprudence and toxic effects of drugs will be studied in the respective chapters of drugs.

Therapeutics : It is that branch of medicine, which deals with the art of healing ; in other words, *applied pharmacology*. Therapeutics are of three types :

(a) *Rational or Pharmacotherapeutics*—dealing with the treatment of diseases by specific drugs, viz. quinine in malaria, emetine in amoebic dysentery, sulpha drugs in infections, digitalis in heart diseases. In all these cases, there is a rational and pharmacological basis of use of drugs and their actions are demonstrated on animals.

(b) *Empirical Therapeutics*. In this case, the drug action is not demonstrable by experiments but the drug is used by the clinicians by convention and from personal experiences. A good number of our drugs come

(c) *Accessory Therapeutics* deal with other means of treatment, viz. (i) *Hydrotherapy*, treatment of diseases by spring water and mud, (ii) *Physiotherapy* treatment of diseases by deep X-ray, radium, ultra-violet and infra-red ray therapies, (iii) *Accessory therapeutic or treatment by massage, dietetics, etc.*

A student of medicine must be familiar with all these aspects of treatment so that, as a doctor, he can manage his patients and alleviate their sufferings even if he cannot cure all of them radically.

Relationship : The subject of pharmacology is related to a number of other medical subjects.



Botany : (a) It has been stated that pharmacognosy is an integral part of pharmacology and in spite of rapid advances in drug synthesis, a large percentage of drugs are still of plant origin. (b) These crude drugs are required to be authentic and of standard quality containing adequate percentage of active principles. They are also to be cultivated under standard conditions. (c) Thus from the standpoint of pharmaceuticals, pharmacognosy and drug cultivation, knowledge of botany is important.

Chemistry : (a) Many drugs are obtained from chemical sources. (b) Drug synthesis and testing are done with the knowledge of chemistry. (c) Mode of action and metabolism of drugs are understood with the knowledge of chemistry. (d) Thus, inorganic, organic, physical and biochemistry—all play vital roles in the study of pharmacology.

Physiology : The subjects of pharmacology and physiology are closely interrelated. (a) Experimental techniques are practically the same for both in eliciting normal functions and drug responses. (b) Pharmacological researches with acetylcholine, atropine, adrenaline, digitalis, vitamins, hormones and radioactive substances and also on excretion of drugs have subscribed to the existing knowledge of physiology by unveiling intricate functions of the body, hitherto not properly understood by other methods of study. (c) Thus both pharmacology and physiology are closely correlated and at certain points they almost lose their separate identity and become fused into one.

Pathology and bacteriology play important roles in the estimation of toxicity, efficacy and also the discovery of newer drugs : (a) Bac-

teriology has contributed to pharmacology in introducing *sera*, *vaccines* and *phages*. (b) Modern chemotherapeutic evaluation of drugs is carried out on inoculated animals. (c) Toxic effects of drugs are also studied by pathological changes in the living organism of animals, by acute and chronic experiments. (d) Knowledge of parasitology is required for the study of anti-parasitic chemotherapeutic drugs.

Medicine : This is on the direct line of pharmacology. Knowledge of diseased processes is essential for understanding the scope of therapeutic uses of a drug, while knowledge of pharmacological actions of a drug determines its rational use in therapeutics.

From the foregoing, it is evident that medical subjects are inter-related and integrated, so that the sum total of the knowledge of allied subjects can lead to the proper diagnosis, prevention, alleviation or cure of diseases, which is the ultimate objective in any comprehensive medical care.

Scope : It has been seen that even 50 years ago, scientific pharmacology played a very minor role in the treatment of diseases, so much so, that the astute but critical Osler, in disgust of the therapeutic nihilism, even in the earlier part of this century, cynically exhorted that '*Tincture Cardamom Co.*' was the only sensible drug in his time, because of its colour, flavour and innocence.

As a result of recent advances in pharmacological researches, leading to the discovery of many potent, and specific drugs from synthetic and biological sources, the scale has completely turned. If the present rate of discovery continues, the future line of progress will be in the direction of specific therapies by : (a) discovery of newer synthetic and biological drugs, (b) exploration of newer medicinal plants unveiling hidden properties and chemical structures, not hitherto known, thus opening newer vistas of drug synthesis, and finally (c) by ensuring easy availability of standard medicinal preparations after accurate chemical and biological testings, possessing desired specificity of action with minimum toxicity.

It is only through researches that appropriate discoveries can be made so that, one day, specific drugs will become available for most of the important diseases, baffling therapeutic measures of today.

Taking into consideration the achievements of the last 50 years, it would appear that this may no more be the idle dream of Galen or of the workers of the middle ages, trying to find out a panacea for all diseases, but by discovery of specific drugs for specific conditions, as has been occurring in recent years.

CHAPTER

2

DRUGS—SOME FUNDAMENTAL ASPECTS

(SOURCES, ACTIVE PRINCIPLES, PHARMACOLOGICAL PREPARATIONS,
DOSAGE-FORMS AND QUALITY CONTROL)

[The word '*drug*', coming probably from its French counterpart '*drogue*' (dried herb), is a chemical substance which modifies existing functions of the body without creating any new one and given in optimal concentrations cures or alleviates diseases without producing any toxic effects. It is obtained from a wide range of sources : *chemical*—organic, inorganic and synthetic ; *biological*—hormones, vitamins, enzymes, sera, etc. and *vegetable drugs*.

Different parts of different medicinal plants—roots, leaves, herbs, flowers, fruits and seeds, are used medicinally, in accordance with their active principle content ; and plants are also cultivated, collected, and stored under specified conditions, so that maximum quantity of active principle without any risk of deterioration is present in the crude drugs used.

The pharmacologically active constituents in medicinal plants are different chemical entities—alkaloids, glycosides, neutral and bitter principles, cellulose, oils and tannins. They are to be present in any medicinal preparation in specified quantities, free from impurities, as prescribed by pharmacopoeial standards for quality control of drugs.

These preparations are obtained by using *pharmaceutical* processes of fusion, granulation, contusion, disintegration, maceration and percolation. The active principles are isolated with different *solvents*—water, alcohol, petroleum, chloroform, glycerine, acetone and propylene glycol, according to the differential solubility of the solute. They are then dispensed in different dosage forms—elixir, emulsion, lotion, mixture, spirit, syrup, tincture, injection, tablet, suppository, pill, powder, lozenge, pellet and capsule.

For the dispensing of drugs by pharmacists, specified weight and measure systems in use are (a) Metric, and (b) Imperial ; the former being used in most of the countries.]

A *drug* is a chemical substance, often a poison, which stimulates, depresses or influences the existing functions of the body by physico-chemical changes without creating any new one. When administered in optimal doses, it should remove or alleviate disease processes without producing any toxic effect on the tissues.

A drug does not supply the caloric requirements to the body and hence it is not a *food*. In therapeutic doses, drugs are intended to

cure a disease without producing any adverse effect and thus not intended to function as *poisons*.

SOURCES

Drugs are derived from a very *wide range of sources*. An analysis of *materia medica* of all the systems of medicine shows that attempts have been made to derive drugs from almost everything out of nature; silica, ashes of pearls, organoleptic drugs are all instances of this. However, since the discovery of *penicillin* from the common fungus, *Penicillium notatum* abounding everywhere, it appears that posterity is likely to reveal the hidden, unknown properties of many a common substances, some of which, one day, may turn out to be life-saving drugs like penicillin.

Drugs are commonly derived from the following domains :

Chemicals : (a) Inorganic, (b) Organic, and (c) Synthetic.

Inorganic : (a) *Alkalies and metals of alkaline earth*—Na, K, Ca, Mg, Ba, NH_4 and their salts. (b) *Acids*—HCl, HNO_3 , H_2SO_4 . (c) *Metals and metalloids*—Pb, Ag, Zn, Cu, Fe and their salts.

Organic : (a) *Compounds of Aliphatic series* : Paraffin, alcohol, ether, chloroform, aldehydes, ketones, fatty acids, unsaturated hydrocarbons, oxalic, citric, lactic and tartaric acids and their salts, are all useful drugs. (b) *Aromatic compounds* : The coal tar derivatives—phenol, cresol, benzene, benzoic, mandelic and salicylic acids—are extremely important drugs in use in medicine. Further, they have been the starting point of *synthetic drugs*.

Synthetic Drugs : These now constitute one of the most important and effective sources of drug supply for specific therapy of diseases.

Chemotherapy started with aniline and that is why, in Germany, the synthetic work is called '*farben industry*'.

- (a) The azo compounds have given the sulpha drugs.
- (b) The quinolines, pyridines, phenanthrenes and tropines have all yielded effective synthetic compounds to medicine.
- (c) Lastly, terpene, camphor and naphthalene derivatives have also wide uses in medicine.

Biological Drugs : Many drugs are obtained from biological sources. They comprise of hormones, antibiotics, sera, vaccines, phages, enzymes and vitamins.

The *hormones* are the internal secretions of ductless glands and

are usually obtained by isolation from cattle glands. Several of them have also been synthesised now. Anterior pituitary, thyroid, corticosteroids, male and female sex hormones and insulin are the important members of hormones in therapeutic use.

A few other substances of *animal origin* are also possessed of medicinal properties and are sparingly used:

- (a) *cantharidin*, obtained from the Spanish fly, *cantharis vesicatoria*, is an irritant and vesicant,
- (b) *musk*, a prepuccial secretion from musk deer, is reputed to be a stimulant,
- (c) *hirudin*, salivary secretion of leeches, is an anticoagulant and
- (d) *snake-venom* from cobra and russel viper is sometimes used for the relief of intractable pain.

Fungal Drugs : To start with, *ergot* was the only known fungal drug in therapeutic use as an uterine tonic but since the discovery of penicillin, streptomycin and other *antibiotics*, the role of a large number of fungi and moulds as sources of many life-saving drugs has been established and many newer potent drugs are being frequently discovered from these microbiological sources.

Vaccines, Sera and Phages : This is another group of microbiological, protein drugs brought into use from the end of the last century.

(a) The *Vaccines* are the dead or attenuated bacteria or viruses or their toxins or gamma globulin, which, after injection, produce antibodies in normal individuals and offer protection against the same infection. Cholera, T.A.B., small-pox, polio and antirabic vaccines are the instances of these.

(b) *Sera* : These are usually horse sera containing antibodies, produced by injections of gradually increasing doses of *antigen* in the form of specific vaccines or toxins in horses. Antidiphtheritic, antidysenteric, antimeningococcal, antitetanic and gas gangrene are the examples of curative sera in use.

(c) *Phages* : These are probably viruses, developing in certain diseases during the process of intestinal infections, which can be isolated and grown in alkaline culture media. They possess lytic properties vis-a-vis the parent organism and have been tried orally as cholera, dysentery, typhoid and enterophages but are now rarely used.

Enzymes : The following bio-catalysts—pepsin, trypsin, papaine, taka diastase—are commonly used.

Vitamins : These form a special group. At first isolated from various foodstuffs and green vegetables, now most of them have been

successfully synthesised. Vitamins are widely used as medicines, both for prevention as well as for cure of deficiency diseases.

Vegetable Drugs : By far the largest number of drugs are still obtained from vegetable sources. Possibly, synthetic drugs will one day deprive them of their privileged position but that will not minimise their importance and role in modern therapeutics, in as much as *drug synthesis* itself has been the outcome of the knowledge of isolated active principles of medicinal plants, their structural study and analysis.

A very important part of the floral wealth of the world is used as medicines all over the world and in India also, we have a large number of *indigenous medicinal plants*. A detailed study of these may, one day, give us newer drugs, hitherto unknown to the world, as in the case of *Rauwolfia serpentina*, the wonder drug for hypertension and mental diseases.

Parts of Plants used Medicinally: The active principles are diffused throughout the plant but certain parts are richer in them than others. The following parts of plants are frequently used for the preparation of medicines :

Root (radix)—leafless, underground part, devoid of chlorophyll—belladonna, rhubarb.

Tuber (tuberum)—bulbous root, a depot of food reserve—aconite, jalap.

Corm (cormus)—thickened underground stem—colchicum.

Bulb (bulbus)—fleshy base stem, enfolded by crowded leaves—onions, squill.

Rhizome (rhizoma)—underground stem bearing leaves—podo-phyllum, zinger, hydrastis.

Bark (cortex)—outer layer of the stem—cinchona, cascara.

Leaves—(folia)—digitalis, belladonna, senna.

Herb (herba)—delicate leafy flowery stem—peppermint, cannabis indica.

Flower (floris)—arnica, cloves, santonica.

Fruit (fructus)—pepper, colocynth.

Seeds (semina)—nux vomica, strophanthus, mustard, linseed.

Cultivation and Acclimatisation of Plants: Like animals, plants also choose certain climates and soils for their growth. Roughly speaking the geographical distribution of plants is as under : (a) *plants growing usually in temperate climates* ; digitalis, male fern, colchicum aconite, etc. (b) *plants usually growing in tropical and subtropical climate* ; cinchona, ipecac, capsicum, etc.

This clear-cut demarcation is now gradually disappearing. With the increased knowledge of soil chemistry and requirements of plants, many drugs which never grew in India are being grown now. Further, study of allied species of plants is enabling many countries to exploit to the fullest extent, their floral resources in medicine.

Collection of Crude Drugs: Like soil, age and season of collection of plants is also of value in the development of medicinal properties in plants :

- (a) *Rhubarb* contains no anthraquinone in winter. China and Turkey rhubarbs, 6 years old, are better than Indian ones.
- (b) *The old cinchona bark* is better than the new ones, as the latter contains much less quinine.
- (c) *Digitalis leaves* should be collected on alternate years and in the afternoon only. At night the glycoside splits off sugar. It should be collected with flowering tops in dry seasons.

Generally speaking, leaves should be collected dry and when flowering, and stems when the plant is withering.

Drying: (a) All moist drugs are liable to fungal growth which destroys the active principles—digitalis, ergot. (b) Quick drying is the best, except in cases of plants which contain enzymes.

Oven drying is the quickest and maintains the colour of plants intact. Open air drying is slow and gradual but more practicable.

A dry plant represents only 10-40 per cent of the initial weight. British Pharmacopoeia allows 10 per cent moisture content approximately in crude drugs in most of the cases.

Storage: Long storage is usually deleterious to drugs. Certain crude drugs are to be stored in air-tight containers, otherwise they lose their property, e.g. ergot, digitalis, Indian hemp.

PLANT CONSTITUENTS—IMPURITIES AND STANDARDS

Different parts of plants are selected for medicinal use and they are also collected and stored under prescribed conditions. This is because crude drugs contain only a small percentage of active principles, unequally distributed in the different parts of the plants in different concentrations along with much undesirable inert substances which are to be eliminated from the medicinal preparations. Further, the active principle content in the plant is also variable in the same and allied species, growing under different conditions.

Plant constituents of medicinal importance form an extraordinarily diverse group of chemical entities with variation in solubility,

stability, etc. Any suitable medicinal preparation should contain minimum of useless substances but optimum quantity of active principle in stable form, well tolerated by the system.

The pharmacologically active constituents in plants broadly come under the following categories :

- (a) Alkaloids, glycosides, neutral and bitter principles and saponins.
- (b) Cellulose, carbohydrates, tannins, gums and resins.
- (c) Oils, fats and waxes.
- (d) Enzymes of pharmacological use.
- (e) Mineral substances of pharmacological value.

Alkaloids. Very important plant constituents, nitrogenous organic heterocyclic bases, generally tertiary amines, which form salts with acids. They are possibly metabolic waste products of plants. The base is often insoluble in water, bitter and soluble in chloroform. The salts are more readily soluble in water. They are precipitated by alkalis, heavy metals, tannins and iodine.

According to their basic nuclei, they can be grouped as :

- (a) Phenylalkylamine—ephedrine,
- (b) Tropine—atropine, cocaine,
- (c) Quinoline—quinine, quinidine,
- (d) Indole—strychnine, ergotoxine, reserpine, yohimbine,
- (e) Purine—caffeine, theobromine, theophylline,
- (f) Phenanthrene—morphine, codeine, thebaine,
- (g) Pyridine—nicotine, lobeline, arecoline.

Names of all alkaloids end in 'ne'.

Glycosides are ester-like combinations of sugars with aglycone bodies. On hydrolysis, they give one or more molecules of sugar. If glucose, it may be called '*glucoside*', but if any other sugar '*glycoside*'.

These are bitter substances, soluble in water and alcohol, neutral or weakly acidic. The pharmacological action is contained in the '*aglycone*' or '*genine molecule*' whereas the sugar molecule helps in the absorption and persistence of actions. The *anthraquinone glycosides* present in rhubarb, senna, cascara and aloes are purgatives. *Cardiotonic glycosides* are present in digitalis, strophanthus and squill.

Neutral and Bitter Principles : These are non-nitrogenous, crystalline substances, responsible for bitter taste of vegetable bitters and cannot be properly classified. These are chireta, quassia, gentian, etc. A good number of them are 'lactones'.

Saponins are also non-nitrogenous principles, allied to glycosides, foam like soap, emulsify fat and produce haemolysis. They are present in senega and quillaia which act as expectorants. Some of them are very toxic and known as 'sapotoxins'.

Cellulose is found in the cell-wall of plants—cotton, agar agar. Chemically, it is an isomer of starch. In older cells, it becomes lignin and cork which are protective layers for plants. With retrograde metamorphosis, it can become gum or pectin.

Carbohydrates like sucrose, starch, honey are used medicinally. *Manna* is a saccharide exudate from *Fraxinus ornus* and is used as a laxative for children.

Gums are colloidal exudates of plants, swelling or dissolving in water. They are formed by pathological changes of cellulose and are related to polysaccharides. They are precipitated by alcohol, and form viscid, adhesive fluid in water, called 'mucilage'. On hydrolysis, they yield simple sugars. *Gum acacia* and *gum tragacanth* are extensively used in pharmaceuticals.

Resins are rosin like substances, which are complex mixtures of resinic acids and alcohol and obtained as exudates after incision of certain plants. They are non-nitrogenous, colloidal bodies, insoluble in water, but soluble in alcohol, e.g. *pine resin*, colophony and cannabiol. *Copaiba* is an oleo-resin.

Balsam is a mixture of resin, benzoic acid and volatile oil. Many extracts contain resins which, when diluted in a mixture, may precipitate, producing unsightly mixtures. Most of them are used as pulmonary and urinary antiseptics. Resins of jalap and podophyllum roots act as purgatives.

Tanins : A group of non-nitrogenous phenol derivatives, astringent and soluble in water and alcohol. Examples are gall nut and catechu. Tannins may be decomposed to resinous matters and are then known as *phlebotannins*.

Oils, Fats and Waxes : There are two types of oils, used as medicine.

(a) *Fixed oils*—non-volatile, bland oil, obtained by expression of oil seeds and used for soothing, demulcent, lubricant and emollient properties. Castor, olive and arachis oils are examples of fixed oils.

(b) *Volatile oils*, also known as *essential oils*, are obtained from aromatic plants by distillation. They are *terpene* or *sesquiterpene* derivatives and do not form soap with alkalis, nor become rancid. They are sparingly soluble in water. Eucalyptus oil and essence of rose are examples of volatile oils.

Fats are vegetable or animal in origin. Coca butter and wool fat (lanolin) belong to this group.

Waxes are derived mostly as animal products, e.g. *beeswax*.

DRUG IMPURITIES

Drug impurities leading to inferior quality of drugs may occur in any of the following ways :

(a) *Imperfect selection*: *Aconite napellus* is official and effective ; *A. heterophyllus* is very little active.

(b) *Imperfect preparation*: Any faulty method of preparation of medicines would allow impurities in the finished product, from—
(i) faulty extraction of active constituents, (ii) defective elimination of inert substances.

(c) *Imperfect preservation* would lead to loss of activity, as for example *digitalis*, *ergot*.

(d) *Deliberate adulteration* from profiteering motive, mixing less costly substances of similar appearance with costly drugs, e.g. *quinine* and *phenacetin* with *calcium carbonate*. Sometimes, '*exhausted drugs*', from which active ingredients have been removed are incorporated, as in the case of *cloves*, *cardamom*, etc.

PHARMACOPOEIAL STANDARDS

Purity and potency of medicinal preparations are ensured by strict adherence to the specifications laid down in different pharmacopoeias about their method of preparation and testing. The important books laying down these standards for various countries are the following :

(a) *Indian Pharmacopoeia* (I. P.), (b) *British Pharmacopoeia* (B. P.), (c) *United States Pharmacopoeia* (U. S. P.), (d) *French Pharmacopoeia* (*Codex*), (e) *German Pharmacopoeia* (*Arznei Buch*), (f) *British Pharmaceutical Codex* (B. P. C.), (g) *Extra Pharmacopoeia*, (h) *National Formulary* (N. F.), (i) *New and Non-official Drugs* (N. N. R.).

The *London Pharmacopoeia* was first compiled in 1618, *U. S. P.* in 1820, *B. P.* in 1864, *B. P. C.* in 1907, *Extra Pharmacopoeia* in 1883, *National Formulary* in 1949, *Indian Pharmacopoeia* in 1955 and *Indian National Formulary* in 1960.

These authoritative compilations have been compiled by special committees after collection of data of chemical and biological tests, carried out in different laboratories under standard conditions. The various standards about drugs and their permissible limits have then been fixed. Of these, the pharmacopoeias are the most conservative and accept only those drugs the efficacies of which have been thoroughly established. *Codex* and *Extra Pharmacopoeia* contain greater number

of drugs, while *N. N. R.* deals with newly discovered drug of promise, which after further experimentation, get a place in pharmacopoeia.

According to whether a drug is included in the pharmacopoeia and other semi-official books, it is known as : (a) *Official Preparations*—included in pharmacopoeia. (b) *Semi-official Preparations*—included in to compose the abbreviating letters as—BPC., NF., EP. (c) *New and Non-official Preparations*—contained in NND. (d) *Proprietary and Patent Preparations*—Special preparations, protected by monopoly and trade mark by the discoverer or manufacturer.

DRUG TESTING

Quality Control: To ensure purity and potency, all medicinal preparations are to be tested, as per standards, laid down in pharmacopoeias, provided a test is prescribed. These tests, as detailed in Chapter 6, are of two types : (a) chemical, and (b) biological. The former aims at determining through *purity, identity* and estimation of *active principles*, its potency, while the latter measures the activity, therapeutic efficiency and toxicity of drug preparations by animal experimentation.

GENERAL PHARMACOLOGY

PHARMACEUTICAL PROCESSES

There are three important types of Pharmaceutical Processes used for the preparation of drugs : (1) Chemical, (2) Comminution, (3) Extraction.

	Fusion	Solid substances liquefied and mixed with heat or steam for making pharmaceutical preparations.	Plasters, Ointments
Chemical Process	Scaling	Concentrated solutions thinly spread over glass plates, dried and made into flat angular glistening scales.	Iron and Ammonium citrate. Iron and quinine citrate.
	Granulation	Conversions of powders in granular forms in a granulator for the preparation of tablets.	P. A. S. Ferrous Sulphate
	Sublimation	Vapourising of solids without liquefaction and condensation to purer forms in sublimation apparatus.	Iodine Sulphur
Comminution Process	Grinding	Reduction of crude drugs to a fine powder by mechanical means like ball mills.	Nux Vomica Ergot
	Contusion	Conversion of slices of crude drugs to powder forms in mechanical mortar and pestle.	Cinchona bark
	Disintegration	Powdering of crude drugs by high speed percussion in a disintegrator.	Nux Vomica Ergot
	Elutriation	Separation of powders of drugs into fine, medium and coarse powders by stirring the suspension and draining at different levels	Chalk Kaolin Calamine
Extraction Process	Infusion	Extraction of a drug with boiled water in an infusion kettle.	Tea Digitalis
	Decoction	Extraction of active principles in boiling water	Gentian extract
	Maceration	Extraction of powdered drugs in suitable solvent for a specified period in maceration vats.	Tincture Digitalis Tincture Benzoin Co.
	Percolation	Successive maceration of powdered drugs placed in layers, through which, the solvent is allowed to slowly pass, as in a percolator.	Coffee Ergot

Plate V

BENZENE	PYRIDINE	PYRIMIDINE
Sodium salicylate ; Sulpha drugs ; Organic arsenicals	Nicotinic acid Coramine	Sulphadiazine Barbiturates
IMINAZOLE	THIAZOLE	NH PYRAZOLE
Histamine Antistine	Sulphathiazole Thiamine	Amidopyrine Butazolidine
INDOLE	QUINOLINE	ISOQUINOLINE
Rauwolfia alkaloids Strychnine ; Ergotamine 5-hydroxytryptamine ; LSD-25	Antimalarials Antiamoebics Local anaesthetics	Papaverine Narcotine
NH PHENOTHIAZINE	ACRIDINE	
Tranquillisers ; Antihistaminics ; Antiemetics ; Antispasmodics	Mepacrine	
CYCLOPENTANO PERHYDRO PHENANTHRENE	PURINE	
Corticoids ; Sex hormones Cardiac glycosides Vitamin D	Caffeine Theophylline Theobromine	

FIG. 19. Some of the important basic nuclei.

SOLVENTS

These are liquid chemicals which selectively dissolve active principles or solutes from a solution for the purpose of isolation.

Aqua	Wide solubility—glycosides, gums, colouring matter, tannins, albuminous matter and ferments. Disadvantage—not a very selective solvent.
Alcohol	More selective than water. It extracts alkaloids, volatile oils, resins and neutral principles. Also acts as a preservative.
Ether, Chloroform and Petroleum	Fat and alkaloid solvent and also preservative.
Glycerine	Solvent, preservative imparting sweet taste to the preparation.
Dilute Acetic Acid	Extracts alkaloids and makes preparation acidic.
Acetone	Fat and resin solvent, unsuitable for internal use.
Propylene glycol	A new important fat solvent. It stands autoclaving and is also a preservative. It is a stable substance and widely used for preparation of certain injections, eye lotions and cosmetics.

IMPORTANT DOSAGE—FORMS AND PREPARATIONS

Aqua aromatica: Saturated solutions of volatile oil or other aromatic substances in water.

Preparations	Dose	Use
Aqua Camphorae Aqua Cinnamon Conc.	15-30 ml 0.3-1.0 ml	Antispasmodic Carminative Flavouring agent
Aqua Chloroformi	15.0-30.0 ml	Flavouring agent

Capsules: A gelatin shell having a body and cap, meant for administration of disagreeable dosages.

Preparations	Dose	Use
Tetracycline	1.0-2.0 gm	Broad spectrum anti-biotic
Benadryl	0.025-0.070 gm	Anti-allergic
Tetrachlorethylene	1.0-3.0 ml	Anthelmintic

Dilute Acids: Strong acids diluted with water.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Acid Hydrochloric dilute	0.6-8.0 ml.	In acid dyspepsia
Acid Phosphoric dilute	0.3-4.0 ml	Tonic

Elixirs: Weak, aromatic tinctures of potent drugs, rendered pleasant by mixing with sweetening agents.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Elixir Cascara sagrada	2.0-4.0 ml	Mild purgative

Emulsions: Aqueous suspensions or dispersions of oily substances with the help of emulsifying agents.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Emulsio Oleo Morrhuæ	15-30 ml	Rickets
Emulsio Oleum Ricini	15.0-30.0 ml	Purgative

Extracts: Contain active principles of crude drugs extracted with water or alcohol. (a) In *liquid* extract, water is the solvent and alcohol is a preservative.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Liq. Extract Cascara	2.0-4.0 ml	Purgative
Liq. Extract Nux vomica	0.6-2.0 ml	Tonic

(b) **Dry:** Alcoholic or watery extracts, dried under reduced pressure and powdered.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Dry Ext. Cascara	0.12-0.5 gm	Purgative
Dry Ext. Belladonna	0.06-0.0160 gm	Antispasmodic

Glycerins: Solutions of drugs in glycerine or glycerine and water, meant for application to the throat.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Glycerini Acidi Tannici	Local application	Astringent
Glycerini Phenolis	-do-	Antiseptic
Mandel's Paint	-do-	-do-

Implants: Sterile cylinders prepared by fusion for implantation under the skin.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Testosterone	0.1-0.6 gm	Impotency

Injections: Sterile aqueous or oily solutions or suspensions of drugs intended for parenteral administration.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Benzyl Penicillin	2.5-10 lac Units	Anti-infective
Quinine dihydrochlor.	300-600 mg	Malaria
Cortisone	50-200 mg	Addison's disease
Emetine HCl	30-60 mg	Amoebic hepatitis
Morphine sulphate	10-20 mg	Analgesic
Nalorphine hydrobrom.	5-10 mg	Morphine poisoning
Atropine sulphate	0.25-1 mg	Antispasmodic
Cyanocobalamine	50-100 ug	Pernicious anemia
Digoxin	2-4 ml	Congestive heart failure
Nikethamide	1-4 ml	Analeptic
Liq. Adrenaline	0.2-0.5 ml	Hypotension
Pethidine HCl	25-100 mg	Analgesic

Lamellae: Thin plates of medicated gelatin and glycerin for ophthalmic use.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Lamellae Atropine	1/100 mg	Mydriatic
Lamellae Physostigmine	1/20 mg	Myotic

Liniments: Liquid or semi-liquid preparations used for external application.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Liniment Camphor	Topical application	Lumbago and deep-seated pain
Liniment Turpentine	-do-	Irritant and rubefacient

Lotions: Aqueous or alcoholic solutions or suspensions of active ingredients in water, meant for external application.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Lotio calaminae	Topical application	Soothing lotion
Lotio Hydrargyri Nigra	-do-	Syphilitic ulcers

Lozenges: Flat tablets meant for slow disintegration in the mouth.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Penicillin	1,000 units	Antiseptic
Tetracycline	"	"
Dequadin	0.25 mg	"

Mixtures: Combination of drugs, dissolved or suspended in water.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Mist. Mag. Hydrox.	4.0-16.0 ml	Antacid and Laxative
Mist. Senn. Co.	30.0-60.0 ml	Purgative

Oculenta: Eye ointments—contain active drug in 90 percent soft paraffin—and 10 percent wool fat.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Oculentum Atropine Sulph.	1 %	Mydriatic
Oculentum Penicillin	2,000 Units/G	Antibiotic
Oculentum Terramycin	3 %	"
Oculentum Hydrocortisone	1 %	Anti-inflammatory

Ointments: Semi-solid or soft preparations containing the active ingredient in paraffin base, for external application.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Ung. Hydrarg. Ammon.	2.5 %	Antiseptic & antiparasitic
Ung. Hydrocortisone acetate	1 %	Anti-allergic
Ung. Acid, Salicylic	2 %	Antiseptic
Ung. Sulphur.	10 %	Antiparasitic
Ung. Penicillin	3 %	Antiparasitic
Ung. Achromycin	3 %	Antiseptic

Pills: Globular masses meant for swallowing.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Blaud's Pill	0.24-0.48 gm	Iron deficiency anaemia

Pulverata: Simple powders of single crude vegetable drugs.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Pulv. Digitalis	1.0-1.5 gm	Cardiac tonic
Pulv. Ipecac.	0.03-0.12 gm	Expectorant & Emetic

Pulvares: Compound powders of two or more crude vegetable drugs.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Pulv. Ipecac. et opii (Dovers powder)	0.3-0.6 gm	Diaphoretic
Pulv. Effervescens Co.	4.0-8.0 gm	Cathartic

Spirits: Alcoholic solutions of volatile oils and ethers—Simple and Compounds.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Sp. Chloroformi	0.3-2.0 ml	Carminative and Anti-spasmodic Diaphoretic
Sp. Mentha pip.	0.3-2.0 ml	
Sp. Aetheris Nitrosi	1.0-4.0 gm	

Suppositories: Solid conical medicated masses meant for rectal use.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Suppos. Glycerini	7 %	Laxative

Syrups: Liquid preparation of drugs containing 66% sucrose.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Syrup Auranti	2.0-8.0 ml	Flavouring agents
Syrup Tolu	2.0-8.0 ml	Expectorant and sweetening agent

Tablets: Flat or Biconvex discs prepared by compression or moulding a drug or a mixture of drugs.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Tab. Digoxin	1-1.5 mg	Cardiac tonic
Tab. Reserpine	0.25-10 mg	Antihypertensive
Tab. Pethidine	25-100 mg	For pain
Tab. Cortisone	50-300 mg	Anti-inflammatory
Tab. Isoprenaline	10-20 mg	Anti-asthmatic
Tab. Aminophylline	100-300 mg	Diuretic
Tab. Phenoxymethyl Penicillin	125-250 mg	Antibiotic
Tab. Isoniazid	100-300 mg	Antitubercular
Tab. Acetazolamide	0.25-1.0 gm	Diuretic
Tab. Chloroquine Phosphate	0.25-0.5 gm	Antimalarial
Tab. Acetyl salicylic acid	0.3-1.0 gm	For pain
Tab. Mepacrine	0.3-0.5 gm	Antimalarial
Tab. Quinine sulphate	0.3-0.5 gm	"
Tab. Quinidine	0.2-0.3 gm	Antifibrillatory
Tab. Dihydroxyquinoline	1.0-2.0 gm	Amoebic dysentery
Tab. Oxytetracycline	1.0-3.0 gm	Antibiotic
Tab. Sulphaguanidine	10-20 gm	Antidysenteric
Tab. Phthalyl sulphathiazole	10-15 gm	Antibiotic

Tinctures: Alcoholic solutions containing active ingredients of drugs prepared by maceration or percolation.

Simple: One ingredient and one solvent.

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Tinct. Nux vomica	0.6-2.0 ml	Tonic
Tinct. Ipecac	0.6-2.0 ml	Tonic
Tinct. Digitalis	0.3-1.0 ml	Cardiac Tonic

Compound: More than one ingredient and one solvent.

Tinct. Benzoin Co.	Local application	Styptic
Tinct. Card. Co.	2.0-4.0 ml	Carminative

Complex: More than one ingredient and solvents.

Tinct. Opii camphorata	2.0-4.0 ml	Expectorant and antidiarrhoea
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GENERAL PHARMACOLOGY
PHARMACEUTICAL ARITHMETIC
(Metrology)

Weights and Measures

There are two systems in use:

(a) Metric System (b) Imperial System

METRIC SYSTEM

<i>Measures of mass:</i>	1 Microgram (μ g)	0.001 milligram
	1 Milligram (mg)	0.001 gram
	1 Centigram (cg)	0.01 gram
	1 Decigram (dg)	0.1 gram
	1 Kilogram (kg)	1,000 grams
<i>Measures of capacity:</i>	1 Millilitre (ml)	1 cc (approx.)
	1 Litre (l)	1,000 ml

IMPERIAL SYSTEM

<i>Measures of mass:</i>	60 grains (grs)	1 drachm
	8 drachms	1 ounce—oz
	16 ounces	1 lb
<i>Measures of capacity:</i>	60 minims (m)	1 (fl. dr)
	8 fl. dr	1 fl. oz
	16 fl. oz	1 pound (O)
	8 pints	1 gallon (C)
	1 gallon	10 lbs

. APPROXIMATE EQUIVALENTS

<i>Metric</i>	<i>Imperial</i>
1 milligram	1/60 grain
1 gm	15 grains
4 gms or 4 cc	1 drachm
30 gms or 30 cc	1 ounce
450 gms	1 lb

FACTORS FOR CONVERTING FROM ONE SCALE TO THE OTHER

To convert gms into grains	x 15.4
To convert ozs into grams (approx.) or mls	x 30
To convert kgms into pounds	x 2.2

DOMESTIC MEASURES

1 Drop	1 minim
1 Teaspoonful	1 fl. dr
1 Dessert spoonful	2 fl. dr
1 Table spoonful	4 fl. dr
1 Wine glassful	2 ounces
1 Tea cupful	4 ounces
1 Tumblerful	8 ounces

LATIN TERMS USED IN PRESCRIPTIONS

q. s. (Quantum sufficiat)	As much as is sufficient
ad (Addendum)	Sufficient to produce
aa (Ana)	Of each
Ss (Semis)	Half
Ft. (Fiat)	Make
m. (Misce)	Mix
mit. tal (Mitte tales)	Send such
a.c. (Ante cibos)	Before meal
b.i.d. (Bis in die)	Twice a day
t.i.d. (Ter in die)	To be taken thrice daily
C. (Cum)	With
C.m. (Cras Mane)	Next morning
p.c. (Post cibos)	After meals
Rep.	Repeat
Signa	Label
St (Statim)	Immediately

CHAPTER

3

MODE OF ADMINISTRATION AND FATE OF DRUGS

[For eliciting any response on the diseased cell, a drug has to come in contact with it in original or modified form. As an alien substance, it has then to be disposed of. The first is influenced by the route of administration and the second is known as metabolism of drug.]

The methods of administration of drugs are numerous and the choice depends upon the solubility, quantity, desired rate of absorption and likely tissue responses.

The two principal routes are *enteral* and *parenteral*—both having advantages and disadvantages in respect of simplicity, safety and speed of action. The other routes, like inhalation, topical application, iontophoresis, implantation and jet-injections, also have their special advantages and limitations.

Metabolism presupposes absorption, distribution, action, biotransformation and clearance. Some of the drugs are destroyed or poorly absorbed by a particular route while others readily so. Some of the dosage forms provide timed release of drugs.

Most drugs are biotransformed in the biochemical laboratory of liver, spleen, kidney and reticulo-endothelial systems by various chemical processes like dealkylation, deamination, oxidation, reduction and conjugation by enzyme systems. The products are then excreted through kidney, G.I. Tract, lungs, saliva and milk in an exponential manner or otherwise. The clearance may be slow or rapid, depending upon the nature of the drug and the tissue response.

Knowledge of these factors are essential for producing and maintaining effective tissue concentration with appropriate initial and subsequent doses, at optimal intervals, so that rational therapeutic, with minimum side effects, becomes possible. The knowledge of biotransformation also permits synthesis of newer compounds better than those already in use.]

Before a drug can produce its actions it must come in contact with the diseased organs of the body. This is dependent on the route of administration of a drug, the exact choice of which is determined by a number of factors: (a) Solubility in water, oil and special solvents; (b) Rate of absorption and excretion; (c) Quantity of drug to be administered; (d) Likely tissue response vis-a-vis a particular substance.

ROUTE OF ADMINISTRATION

The routes used for the administration of drugs are many but the two most important ones are *enteral* or oral and *parenteral* or by injection.

Oral, also known as 'ingestion', is most ancient and convenient.

Merits: (a) Slow and steady absorption in most cases; (b) Safety valve action of the G.I. Tract; (c) Advantage of local action on mouth, stomach, intestine.

Demerits: (a) Not a route of emergency, and irritating substances may be rejected, e.g. *quinine*, *salicylates*; (b) Some drugs may be destroyed by digestive ferments, e.g. *adrenaline*, *acetylcholine*, *insulin*; (c) Intestinal absorption may sometimes be variable and quantity absorbed is not always predictable, e.g. *calcium*, *iron*.

Parenteral, i.e. not intestinal, involving techniques requiring medical help and there is risk of sepsis and local reactions.

Intradermal, i.e. between the two layers of the skin. Little used and only a few drops can be given. *Small-pox vaccination* and *Schick test* carried out by scarification of skin.

Subcutaneous (S.C.): (a) Only for drugs which do not irritate and slough tissues. (b) Absorption—steady and sufficiently rapid. (c) Only small quantities of drug (1-2 ml) can be administered. (d) *Insulin* and many other drugs, prescribed in small quantities, are given by this route.

Intramuscular (I.M.): Larger quantities of drugs and even irritating substances and oily preparations can be given by this route, e.g. *glucose*, *quinine*, *bismuth*.

Intravenous (I.V.): (a) Optimum concentration, immediate action and toleration of irritating substances are some of the advantages. (b) *Demerits:* (i) Once given, the drug is out of control; (ii) Risk of haemolysis, venepuncture, necrosis and venous thrombosis; (iii) Also fluctuating concentrations.

Intrathecal: Injection of a drug in the subarachnoid space for local action on meninges, e.g. *antimeningococcal serum*, *spinal anaesthesia*.

Intraperitoneal: Provides large surface for absorption but seldom used due to risk of sepsis.

Intracardiac: Used in cases of extreme urgency, e.g. intracardiac *adrenaline* in sudden cardiac arrest, as in drowning.

Inhalation: Volatile substances can be given by this route for quick action—*general anaesthetics* and also *amyl nitrite* for angina pectoris, for immediate result.

Topical: In this case, a drug is intended to produce local effects on skin or mucous membrane.

(a) For skin, *ointments* and *lotions* are used. An ordinary ointment produces *local effects*, blue ointment is partially absorbed and

can produce *systemic effect*, and a *counter-irritant* irritates the skin and produces *remote action*. by axon reflexes.

- (b) For *mucous membrane*, paints, gargles, eye, ear and nose drops and ointments are used. Action is mostly local but a small quantity may be absorbed and produce systemic action. *Sublingual* route of administration of isoprenaline and glyceryl trinitrate permits slow and steady absorption with possibility for rejection when any untoward effect first appears.

Intrarectal, also known as *enema*.

- (a) *Local action*: *Yatren enema* for amoebiasis, *evacuant enema* for unloading the rectum and *hypertonic saline* or *quassia enema* for thread worms.
- (b) *Systemic action*: *Paraldehyde* as hypnotic, or *nutrient enema*, e.g. glucose as retention enema.

Iontophoresis: By this method, certain drug solutions are brought in contact with the skin or mucous membrane and *galvanic current* passed. Ionic dissociation takes place and the drug penetrates into the tissue more easily.

Jet injection: Injection of drug solutions by means of a high velocity jet, projected through a microfine orifice. Needle is not used. Efficacy is equal to that of S.C. injection.

It is useful for *mass inoculation* in immunization programmes, e.g. *typhoid*, *diphtheria*, *tetanus* and *small-pox* vaccinations.

METABOLISM

The process of *metabolism of drugs* refers to the changes undergone by a particular drug in the body. Originally, it meant changes by which a drug was rendered less toxic. However, it became apparent that a number of substances were converted into compounds considerably more toxic than the original drug. As a result, the term "*detoxication*" has been broadened to include all those chemical changes which organic compounds undergo in the animal body, rendering them inactive. Recently, it has been observed that in some cases, a metabolic change in the body creates a *more active drug* from the original compound and to include such changes, the term detoxication has again been redesignated as '*biotransformation*' or chemical modification of drugs by a series of biochemical reactions in the body. For understanding drug metabolism, the following are to be considered:

- | | | |
|-----------------------|----------------------------|------------|
| (1) Absorption | (2) Distribution | (3) Action |
| (4) Biotransformation | (5) Clearance or Excretion | |

The term disposal, referring principally to clearance or excretion, is not synonymous with biotransformation which is concerned only with the chemical changes, undergone by drugs in the body.

Drug metabolism is a vast subject, varying in each group of individual members. This will be discussed in details individually. It is only proposed to outline the general principles here.

Absorption: Before a drug can produce any systemic action, when given by a route not intended for a direct or local effect, from the site of introduction, it has to be absorbed. Absorption depends on a number of factors some of which are discussed below.

Route of administration: The rate of absorption of a drug and the promptness or otherwise of its action vary according to routes of administration. The most prompt and intense action is obtained when the drug is administered by the intravenous route. Effect after oral administration is less prompt.

- (a) *Adrenaline, penicillin and hormones* are absorbed better and act quicker after injection.
- (b) *Sulpha drugs* are absorbed satisfactorily from the intestine also.
- (c) *Anaesthetic gases, oxygen and amyl nitrite* are very quickly absorbed by inhalation.
- (d) *Quaternary ammonium salts* are poorly absorbed from the gastro intestinal tract.
- (e) Drugs in combination with oily or fatty bases, e.g. *penicillin in oil* and *adrenaline in oil* are slowly absorbed after injection.

Solubility and physical state: Solubility in water or oil and physical state of a drug, in many cases, determine the rate of absorption. Soluble drugs are more quickly absorbed than insoluble ones and colloids less readily than crystalloids.

(a) Sodium salts of sulpha drugs and barbiturates which are soluble in water are better absorbed.

(b) Barium sulphate, being insoluble in water, is used for radio-graphic study. If barium chloride is used, gross toxic effects are produced.

(c) Vitamin K is given with bile salts for better absorption.

(d) Combination with procaine as in procaine penicillin or with protamine-zinc as in P-Z insulin delays absorption.

In general, it may be stated that, in oral preparations, the rate for absorption decreases in the following manner:

Solution → suspension → capsule → compressed tablet → coated tablet.

The absorption through membranes occurs readily if the drug is

present in unionised form, provided the unionised form is lipid-soluble. The absorption of both hexamethonium and sulphaguanidine is poor after oral administration; the former is a cation, and the latter, though unionised, is not lipid-soluble. The degree of ionisation is dependent on the pH of the media. Thus the acidity of the stomach or the alkalinity of the intestine modify the absorption of various drugs.

Concentration: Usually concentrated solutions of drugs are more rapidly absorbed than the dilute ones. That is why alcohol is taken in diluted form for drinking. This is not the case with hypertonic saline which acts by osmosis and is much less absorbed than isotonic saline. There are thus many other factors which also come into play.

Absorbing surface: Available absorbing surface is an important factor. Pulmonary endothelium, peritoneal cavity and I.M. spaces absorb larger quantities of drugs as they have larger surface area for absorption.

Vascularity of the absorbing surface: A local anaesthetic combined with adrenaline is absorbed more slowly due to vasoconstriction whereas massage after I.M. injection, accelerates the rate of absorption by producing vasodilatation.

Dosage forms: The rate of absorption of a drug can be varied by administration of different dosage-forms. A number of preparations are available, which are described as 'long acting', 'timed release', 'programmed release' and 'delayed release'. In some cases, they are designated as 'depôt drugs'. Tablets containing several layers have been made, one of which dissolves rapidly providing the initial dose while others dissolve slowly, supplying the supplemental doses, e.g. Sulspan and Peritrate Tablets. Applications of coatings of various thickness have also been used for releasing the drugs at different rates for absorption, e.g. Pyribenzamine and Teesol tablets.

Distribution: After absorption a drug rapidly passes out of the circulation, is distributed within the body fluids and ultimately arrives at the site of action. To achieve an effective concentration at the site of activity, a drug has to cross a number of hurdles—skin, gastrointestinal epithelium, lining of the respiratory tract, R.B.C. membrane, placental barrier, blood-brain barrier and blood-aqueous-barrier.

The distribution of drugs is not always uniform and is often unique for a given agent, as detailed below:

- (a) *Ethyl alcohol* is uniformly distributed,
- (b) *Bromides* are confined to C.S.F.,
- (c) *Trypan blue* is confined to circulatory system only,

- (d) *Digitalis* is selectively fixed to cardiac tissues,
- (e) *Anaesthetics* and *thiobarbiturates* are taken up by adipose tissues,
- (f) *Iodine* and *lead* are selectively concentrated in thyroid and bones, respectively,
- (g) *Amino acids* can pass blood-brain barrier, while amines cannot, e.g., 5-hydroxytryptophan, and 5-HT,
- (h) *Penicillin* crosses the blood-brain barrier poorly while *sulphadiazine* more readily,
- (i) *Chloroquine* is more concentrated in the liver and therefore used for hepatic amoebiasis.

The site of maximum concentration of a drug in the body may or may not be in the tissues upon which it exerts its action. Several drugs are concentrated in the liver and kidney which are not the sites of their action.

Action: With distribution, the drug action is initiated. A drug does not change the character of the function of a system upon which it acts. It either increases the functional activity of the system or diminishes it. Frequently, the character of the action refers specifically to one system of the body and other systems may even respond differently to the same drug. This will be discussed in detail in Chapter 4.

Biotransformation: The changes undergone by drugs in the body are primarily intended for rendering the toxic drugs less toxic or atoxic, before they are eliminated by a series of biochemical reactions. Not infrequently, a drug may even be changed to a more toxic or more active form, if this helps in the process of quicker elimination and thus prevent toxic manifestations.

Usually, the site of detoxication is primarily in the microsomal enzyme systems of the liver and also in the R.E.S. but it may also occur in the kidney, spleen and other tissues. The process of biotransformation is catalysed by a number of enzyme systems, located in these organs and concerned with dealkylation, deamination, hydroxylation, nitrogroup reduction, etc.

All these changes occur with restricted chemicals and reagents, under low thermodynamic conditions, mostly with the help of enzymes.

The products of biotransformation are then excreted from the body either as such or after conjugation. Various biochemical reactions involved in the biotransformation of drugs are given below.

Oxidation: This is an important process of adding of oxygen or removal of hydrogen from the compounds: (a) Alcohol is oxidised

to acetaldehyde (toxic). (b) Adrenaline to adrenochrome (inert). (c) Acetanilide to p-acetamidophenol (active). (d) Short-acting barbiturates to corresponding keto and hydroxy barbituric acids (inert). (e) Parathione to paraxon (more active). (f) Quinine to haemotinic acid (inert).

Hydrolysis: In this process, H_2O is added to the compound which considerably reduces its activities: (a) Acetylcholine is hydrolysed to choline and acetic acid. (b) Aspirin to salicylic acid (less active). (c) Benzyl penicillin to penicilloic acid. (d) Procaine to PABA, but procainamide, used in cardiac arrhythmias, is resistant to this change. (e) Heroine to morphine.

Reduction: Few drugs undergo reduction in the body and in many cases it is an intermediate stage in the metabolic process: (a) Chloral hydrate to trichlorethanol. (b) Pentavalent organic arsenicals to trivalent arsenoxide. (c) Folic acid to folinic acid.

Conjugation: This is referred to as a transfer reaction. Drugs are biotransformed by combination with other chemical substances and are excreted as conjugated products. The conjugation is mostly with the following substances:

(a) Glycine conjugation, e.g. benzoic acid \rightarrow hippuric acid, or nicotinic acid \rightarrow nicotinuric acid.

(b) Glucuronic acid: This combination is the commonest type. Many drugs and poisons are excreted in this form. The metabolic product is known as *glucuronoid*. Phenol, steroids, adrenaline, camphor, morphine, salicylates, sulphonamides, are commonly excreted in this form.

(c) *Sulphate conjugation:* Phenolic compounds, simple aliphatic alcohols and aromatic amines often form conjugates with sulphates, e.g. adrenaline \rightarrow phenol.

(d) Acetic acid conjugation: This is commonly seen in cases of sulphonamides.

Dealkylation: This change involves removal of an alkyl group: (a) Ephedrine to nor-ephedrine. (b) Methyl phenobarbitone to phenobarbitone. (c) Phenacetin to N-acetyl paraminophenol. (d) Aminopyrine to aminoantipyrine. (e) Morphine to nor-morphine. (f) Nicotine to nor-nicotine.

Deamination: This change involves the removal of an amino group, e.g. amphetamine to benzoylmethyl ketone.

Oxidative deamination: This process involves the removal of amino group with simultaneous oxidation: (a) Histamine to imidazol acetic acid. (b) 5-HT to 5-hydroxy indole acetic acid. (c) Adrenaline to hydroxy mandelic acid.

Methylation: Addition of methyl group to the compounds, e.g. arsenicals to dimethyl derivatives.

Hydroxylation: Addition of an OH group, e.g. acetanilide to para-hydroxy acetanilide.

Cyclization: Ring formation as in the case of paludrine, which is thus converted to an active compound.

Flocculation: This is a special phenomenon by which certain substances are aggregated and eliminated as inactive substances: (a) Toxin—antitoxin reaction. (b) Antigen—antibody reaction.

There are, however, many drugs, which resist alteration or degradation and remain active till they are completely excreted. Volatile anaesthetics and quaternary ammonium compounds are examples of this.

The above knowledge has a further significance in that when drugs like arsenicals, chloroform, etc. are administered for therapeutic purposes, the condition of the detoxicating organ must be taken into consideration, so that further damage is avoided.

Clearance: Side by side with the detoxication of drugs, the body tries to get rid of them. Each drug is excreted in a characteristic manner. Certain drugs are eliminated by one obligatory channel, whereas others by a number of routes.

(a) Alkaloids are mostly excreted unchanged through kidneys.

(b) Opium derivatives and heavy metals are excreted mostly through colon.

(c) Bromides are excreted also through sweat and thus sometimes bromide rashes and dermatitis occur.

(d) *General anaesthetics* and *volatile substances* are excreted through lungs and therefore their rate of excretion is extremely quick.

(e) *Anthracene purgatives*, *alcohol* and *belladonna* are excreted also through milk and may thus produce mild drug action in breast-fed babies.

(f) *General anaesthetics* and *morphine* can cross the placental barrier and may produce effects on foetus.

(g) *Mercurial preparations* and some of the *antiepileptic drugs* are excreted also through mouth and this causes salivary and gingival troubles.

However, in spite of all these different channels of excretion, kidneys, colon and alveolar surfaces rank high for the excretion of the majority of drugs. They are consequently susceptible to the damaging influence of certain drugs.

Like the organs for detoxication, the organs of excretion also have

a greater concentration of drugs than in the blood and this is of special value in the case of the following: (a) Tetracycline, streptomycin and sulpha drugs are concentrated in the urine and act as *urinary antiseptic*. (b) Volatile oils like creosote, during elimination through the lungs, act as *pulmonary antiseptics* and *expectorants*. (c) Diuretics concentrate in the kidney and increase the volume of urine. (d) Choleric, during elimination through bile, directly act on the gall bladder and increase the flow of bile. (e) Chloroquine is extraordinarily concentrated in the liver without damaging its tissues and this explains its special amoebicidal effect in amoebic hepatitis.

Exponential Clearance: The word '*exponential*' is derived from the Latin roots—Ex-ponere, meaning, explaining or illustrating. In algebra, it means a symbol showing what power a quantity is raised to an index.

Certain drugs which are very rapidly excreted, may have an excretion directly proportional to their blood concentration at a uniformly fixed rate in an unit of time. For example, if a drug has a rate of 25% clearance in 1 hr. of the quantity present in the body and if initially 100 mg of the drug is given, 25 mg will be excreted in 1 hour and 75 mg will be left. In the 2nd hour, 25% of 75 mg, i.e. 18.75 mg will be excreted leaving behind 56.25 mg. Thus, after a single administration, the rate of excretion will show a decrease which would be logarithmic, i.e. linear as against sigmoidal, in the arithmetic scale. This sort of clearance is called '*exponential clearance*'.

The practical application of the knowledge of drug metabolism is enormous and permits us to work out the *initial loading dose* for initiating drug action and thereafter the reduced dosage schedule for maintenance of the above tissue concentration constant, till the disease is fully under control. The rates of absorption and clearance also enable the doctor to work out a *suitable interval-schedule* for repetition of the dose. Further, the concentration of the drug in the tissues and body fluids and its concentration in the excretory organ, rightly suggest the possibility of effectiveness of a drug against a particular infection. The rate of clearance of a drug also indicates as to whether the drug is a cumulative poison. Thus sulphonamides, penicillin and salicylates are prescribed every 3 hours, while bismuth and thyroxine, because of their slower excretion, are administered much less frequently, only once or twice a week.

All these elaborate knowledge is intended for producing an optimal concentration of a particular drug in the body for a specified period for combatting diseases without producing any organotropic action.

The above knowledge is not only essential for scientifically understanding the intricate mechanism of drug action in the body but the knowledge of biotransformation also permits newer orientation in *drug synthesis*, resulting in the discovery of further specific drugs with less toxicity in certain cases.

CHAPTER

4

NATURE AND MECHANISM OF DRUG ACTION: CELL DRUG INTERACTION CELLULAR PHARMACOLOGY

TYPES OF ACTION: MOLECULAR CONCEPTS: THEORIES

[Nature of drug action, as attempted to explain in a simplified manner by *stimulation*, *depression*, *irritation* and *anti-infective* action, is a broad generalisation and does not meet with the complexity of the problem, requiring understanding of the *cell* as a biophysical unit for drug action, and the *drug* the chemical agent, altering its function by different biophysical mechanisms.

For understanding the *cell*, in the light of the recent advances, is to conceive it with all its complex living processes in dynamic equilibrium, regulated by enzyme governors. The roles of plasmatic membrane, active patches, membrane and end-plate potentials, metabolites and enzyme-substrate reactions, are now established. Similarly, physiochemical concepts of drug action, encompassing biotransformation, dissociation, chelate formation, chemical composition, roles of various groups in modifying drug action, isomerism and spatial orientation of molecules, are equally important.

All these have brought into our purview various theories of physical and chemical action, salt and ionic action, enzyme inhibition and substrate competition, biological antagonism and anti-metabolites action and given us intricate knowledge of '*cellular pharmacology*,' leading to the understanding of specific action of drugs in various fields thus leading to the path of discovery of specific drugs for many conditions hitherto unknown.]

The nature of drug action, for obvious reasons, is extremely complex, as it has to interfere with the complexly adjusted functions of the organism. Drugs are capable of producing responses to various systems of the body which are more or less characteristic of each agent. They are not capable of creating any new function but only modify the existing ones in a manner that the result of the interaction is beneficial to the body.

NATURE OF GENERAL ACTIONS

Actions of drugs are brought by a number of fundamental mechanisms, resulting in some of the following modes of general actions:

(a) stimulation,

(c) irritation,

- (b) depression,
- (d) replacement,
- (e) anti-infective action.

Stimulation: This indicates an increase in the activity of specialised cells. It is an augmented function, commonly used to restore the system, depressed by pathological changes or by drugs, to normal physiological functions. Over stimulation, however, may cause toxic manifestation.

Drugs act with remarkable specificity in stimulating the functions of various physiologic systems:

- (a) Caffeine stimulates cortical and medullary cells.
- (b) Strychnine increases the reflex activity of the spinal cord.
- (c) Adrenaline is a stimulant of the sympathetic receptor organs.
- (d) Acetylcholine acts as a stimulant of the parasympathetic nervous system.

Overstimulation may sometimes result in the depression of functional activity. Very high doses of acetylcholine may cause ganglionic blockade also.

Depression: This refers to decreased activities of the specialised cells. It is a definite type of pharmacological action and is not the after-effect of stimulation. This is utilised for restoring an overstimulated system by disease or drug to the normal physiological function and also for depressing the normal system for therapeutic purposes.

- (a) General anaesthetics and hypnotics depress the cortex and produce unconsciousness and sleep.
- (b) Codeine depresses the cough centre and is used as an anti-tussive drug.
- (c) Trimethadione depresses the activity of the motor cortex and is used in petitmal epilepsy.
- (d) Atropine depresses the activity of the parasympathetic receptor cells and produces an endorgan competition with acetylcholine, thereby making it ineffective.

Irritation: A type of nonselective action, resulting in excessive stimulation, followed by damage or destruction of cells. Irritation in a mild form can be used as a means of stimulating functions. This type of action is sometimes used,

- (a) for stimulating the formation of new tissues for the healing of indolent ulcers, e.g. silver nitrate and mercuric oxide.
- (b) irritant cathartics produce their actions in a similar manner.

- (c) irritants, like silver nitrate, trichloroacetic acid, zinc chloride, caustic soda and inorganic acids, in varying concentrations, produce inflammatory, caustic or corrosive effect.

Replacement: This refers to the use of vitamins or hormones in the treatment of their deficiency disorders. It is, therefore, known as *substitution therapy*.

- (a) Insulin in diabetes.
- (b) Thyroid powder in cretinism or myxoedema.
- (c) Oestrogens and androgens in gonadal insufficiencies.

Anti-Infective Action: In this case, the action is produced against invading organisms, the drugs showing selective toxicity to the organism, compared to the host. The value of the drug depends on the ratio between MTD : MED (maximum tolerated dose, as against minimum effective dose). This is known as "Therapeutic Index" indicating, 'The margin of safety' which should not be less than 3.

The anti-infective action may be specific against some organisms, e.g. chloroquin in malaria and penicillin in syphilis or it may be nonspecific as is often the case with local antiseptics. The action may be bactericidal or bacteriostatic, depending upon the susceptibility of the organisms as against the tissues of the host. In the former case, the action results in the death, while in the latter, inhibition of growth and multiplication of organisms.

All these actions, however, are of quantitative nature and according to our present knowledge, no drug is capable of creating any new function in the body. This is a limitation in drug action and consequently, the popular saying : "Drugs sometimes cure, often relieve and almost always console the patients."

The above simplified views about drug actions, in a general manner, are not fully acceptable in the light of phenomenal advances in our knowledge of biochemistry of cells as well as chemistry of drugs and their mode of action.

It is now an established fact that any drug action involves absorption and diffusion, regulated by a number of complex mechanisms, pertaining to cells which are the ultimate sites of action and also to the solubility, structural changes, spatial configuration, etc. of the drug molecule, permitting a '*required fit*' on the receptors of cells. Some drugs may act from the extracellular fluid, others by acting on the cell membrane and still others intracellularly.

CELLULAR PHARMACOLOGY

This new branch of study refers to the concept of drug action at the cellular level. For this, the cell, which is the *responding system*, is considered to be a bio-physical unit and the drug molecule altering its functions by physico-chemical mechanisms, as the *stimulus* for the action. It is proposed to review the subject, in the light of our present knowledge, under the following heads.

- I. Biophysical concept of *Cell*.
- II. Chemical nature of *Drug*.
- III. Nature and Mechanism of *Drug Action*.

I BIOPHYSICAL CONCEPTS OF CELL

Due to the pioneer work of A.J. Clark, Lechatellier and others, it is now conceived that the living cell is a complex colloidal dispersion of fat, protein and carbohydrate, in dynamic equilibrium of chemical reactions, obeying physiochemical laws and regulated by enzyme governors. As aptly stated by Clark, it is a biologic device to convert foodstuffs of a higher energy to a lower energy level by utilising oxygen and giving off carbon dioxide. The life process of a cell has to function within comparatively narrow limits of thermodynamic environment. It is thermolabile and sensitive to pH changes. Energy is supplied to the cell by oxidation of foodstuffs and they may be disturbed by drugs acting at different strategic points—effector organs, cell membranes and cytochromic constituents like enzymes, substrates, etc. Recent advances in microinjection techniques, isotopic studies, quantitative estimation of drugs fixed on different parts of the cell, as well as their rate of action have revealed much useful information in this respect.

1. *Plasmatic membrane*: It has a definite structure, composed of lipoprotein. The lipid film is not continuous but is interrupted by small water-filled pores or channels and has been described as a *lipoid sieve membrane*. Lipoid soluble substances are believed to diffuse easily through this membrane, while for water soluble substances, special transport mechanism or penetration through the water-filled pores, is required. The cytoplasm of the cell also presents a definite protein-mosaic. The introduction of a drug or any other foreign matter causes a reorientation of the mosaic like the various parts of *jigsaw puzzle*.

The plasmatic membrane shows a high degree of selectivity for ions, potential foodstuffs and drugs:

- (a) The R.B.C. is impervious to Na but allows K, Cl and Br.
- (b) The plasmatic membrane of the amoeba prevents entry of eosin dye into the cytoplasm but after death, it can easily permeate.
- (c) Narcotics and HCN do not produce their specific effects when injected into the cytoplasm of amoeba, but the action is produced if the organisms are immersed into the solutions of these substances. The concentration of these drugs required to produce action indicates that probably they exert their action by forming a uniform monomolecular layer around the cell.

In contrast to a crystal, which represents a repetitively designed tapestry, cell of the organism is not the mere repetition of the same theme and has to be viewed as a whole. The cell and the cytoplasm also continuously undergo exchange of constituents for the transfer of energy. "The food of the cell of today is the membrane of tomorrow and the liberated CO_2 of a later period."

The process of adsorption plays an important role in attracting the molecules on the surface of the cells. The greater the surface area exposed, the greater is the degree of adsorption. It is likely that adsorption, occurring on the membrane surface, initiates many reactions that are vital and causes changes in surface tension and cellular consistency.

With increased knowledge of mode of action of drugs on cells, it has now been established that there is a close relationship between cells and drug molecules for eliciting a drug response.

A man of 70 kg has a total number of 3×10^{13} cells.

A substance of 200 mol. weight has 6×10^{23} molecules in 200 gm.

\therefore 1 gm has 3×10^{21} molecules or 1 mg has 3×10^{18} molecules, providing

$$\frac{3 \times 10^{18}}{3 \times 10^{13}} = 10^5 \text{ molecules of drug per cell of the body.}$$

2. Active patches and drug receptors: Though majority of drugs act on the plasmatic membrane by producing a monomolecular layer on its surface, there are definite evidences on the existence of active patches on this membrane. It is well established that whenever any physiochemical reaction takes place with inanimate objects like metals—copper, platinum or charcoal—they occur at active adsorbing centres of these catalysts. In a similar manner, it is now believed that quite a large number of drugs is also adsorbed on certain specialised areas of cell surfaces, known as 'active patches'. They may be special protein molecules or enzymes, acting as receptors of the cells for natural substrates or drugs.

Drug receptors: The cell component directly involved in the action of a drug has been more recently described as drug receptor. These are chemical entities participating in drug-receptor combination and allowing drug to reach the site of action. Although receptors of most of the drugs are yet to be identified it has been established that drug-cell combinations obeying mass law kinetics are involved in drug action.

Receptor groups which take part in actions of many drugs include carboxyl, amino, sulphhydryl and phosphate groups, spatially oriented in a pattern for reacting with drugs.

Classification of receptors: With the advancement of chemistry of drugs and the receptors, it is becoming evident that different types of receptors are available in the body reacting differently with the same drug. Originally these drug receptors were designated as excitatory or inhibitory depending upon the effects of the drug. These receptors are more clearly characterised on the basis of the effects of specific *agonists* and *antagonists*. The receptors of acetylcholine are now classified as *muscarinic* and *nicotinic* and the receptors of adrenalin are designated as *alpha* and *beta* receptors on the basis of effects of sympathomimetic amines and adrenergic blocking drugs.

A difference between the activity of drugs on the cell membrane and the cytoplasm has been established by the micro-injection technique.

(a) Narcotics like octyl alcohol produce action on amoebae by their presence in the extracellular fluid and this is lost when the drug is injected into the cytoplasm.

(b) Methylene blue similarly produce atropine-like action on frog heart, which is lost on introducing the drug into the cytoplasm or when it is withdrawn from the extracellular fluid.

The presence of active patches is further substantiated by the fact that some drugs act in such surprisingly low concentration that there may not be enough molecules of the drug available to cover more than a small fraction of the area of the cell membrane.

The experiment of Clark with ouabain on frog ventricle is in support of this hypothesis.

Mol. wt. of Ouabain is 760.

∴ 2 ug. contains 2×10^{15} molecules

1 gm. of frog's ventricle contains 3×10^8 cells

∴ 2 ug of drug is fixed by one gram of tissue or 10^7 molecules cell

One molecule of ouabain covers an area of 500 sq. Å²

∴ 10^7 molecules can spread over an area of 5×10^9 sq. Å²

Each cell of frog ventricle has an area of 2×10^{11} sq. Å²

∴ Ouabain absorbed on the cell surface covers $\frac{5 \times 10^9}{2 \times 10^{11}} = 2.5\%$ of surface area indicating that the action is on localised areas or active patches.

3. *Bonding*: It is now believed that the adsorption of a drug on the active patches of the plasmatic membrane of a cell is necessary to evoke a response. Many types of union or bonding between the drug molecule and the enzyme of the active patches have been suggested.

It may be a simple attraction between atoms and molecules as in Vander Waals' bond, which is weak or it may be through hydrogen or ionic bonding. Chemical compound formation by electron transfer appears to be unnecessary for the above.

The above observations have brought pharmacologists to the concept of relationship between '*Dose and Response*' which is exponential, and in log scale, linear and thus *quantitative*.

4. *Membrane and Endplate Potential*: Cell membrane acts as a barrier to substances producing different ionic concentrations between cytoplasm and extracellular fluid. In this manner, a membrane potential is established at the cell surface, which accounts for stimulation or depression. The activity of the cell is associated with depolarisation which is followed by repolarisation. The endplate potential, which refers to skeletal muscle only, is a gradually decaying depolarisation of muscle membrane. Drugs may produce their effects by modifying this membrane-potential.

- (a) Acetylcholine, applied locally on the endplate, produces propagated responses, the contractions being due to local depolarisation.
- (b) Curare and Flaxedil produce paralysis by impeding endplate depolarisations.
- (c) Local anaesthetics and antiepileptic drugs produce their characteristic effects by stabilising the membrane potential.

Though a fascinating hypothesis, it is not yet clear whether the potential change thus produced are causes or resultants of drug action.

5. *Enzymes*: Almost all biochemical reactions in the cell are controlled by the activity of enzymes. They are either present on the cell membrane or form part of the cytoplasm. The surface of the enzyme may act as an active patch or specific receptor for drug action. They consist of protein and various accessory substances which control the activity of the enzyme. If this is a simple ion like copper, zinc, cobalt, magnesium, it is called a cofactor and if this is a complex organic substance, nonprotein in nature, it is referred as coenzyme (Vitamin B₁, B₂, B₆, etc.).

The substance, upon which an enzyme acts, the *substrate*, is absorbed on this active sites at the surface and the action is produced. If these active sites are not available to the substrate, the catalytic action of the enzyme is lost. Drugs inhibit *enzyme-substrate reactions* by specifically inactivating the enzyme either reversibly or irreversibly. The degree of specificity of an enzyme is related to the configuration of the active centre where it activates the substrate. If formation of the enzymes—substrate complex or the activation of the substrate is prevented, specific inhibition of the enzyme may take place. This occurs if

- (a) the substrate or the coenzyme is unable to reach or combine with the active centre, or
- (b) coenzyme prosthetic group or active centres are so altered that these can no longer function normally.

The energy, produced in the cell by oxidation—reduction reactions, is controlled by enzymes. There are two distinct components:

- (a) combination of the enzyme with a substrate to form an enzyme—substrate complex, and
- (b) decomposition of the newly formed complex to liberate the enzyme for reacting with substrate *de novo*.

In addition to the *enzymes*, the role of *Chromosomes* and *Genes*, in the control of cellular activities is extremely important. Recent work in this field indicates that the 23 pairs of chromosomes per cell and thousands of genes on them are not only implicated in carrying the hereditary traits but are also involved in protein synthesis, as well as, overall control of cellular function through the RNA, DNA and ribosome systems.

II. PHYSIOCHEMICAL CONCEPTS OF DRUGS

Since the process of life is governed by physical and chemical changes in the constituents of the cells, it is evident that a drug will ultimately produce its action by influencing the physiochemical set up. Drug action is produced either on the surface or after penetration into the interior of the cell, resulting in chemical, physical or biological modifications of their functions, depending on a large number of factors:

- (a) Biochemical changes.
- (b) Concentration.
- (c) Dissociation.
- (d) Chemical constitution.

Biochemical changes: It is an established fact that the human body as indicated earlier, is a great biochemical laboratory, which utilizes chemical, physical and other processes for elaboration of newer com-

pounds. The drug may be rendered more active, more toxic, less toxic or altogether converted to a different form making it more suitable for a perfect fit with the effector cells or its enzyme system.

It has also been noted that many drugs are changed to other forms—Prontosil to sulphanilamide, folic acid to folinic acid and paludrine to dihydrotriazine compound, which are much more active than the parent substances.

Similarly, *chelate formation* by salicylates, paludrine and tetracycline accounts for their mechanism of action.

Concentration: A number of factors determines the effective concentration of a drug at the site of its action. These are: (a) solubility, (b) diffusion, (c) partition coefficient, and (d) ability to traverse physiological barriers.

After absorption, the drug passes into the tissues through the capillary walls. The mechanisms by which substances cross cell membranes are: (a) simple diffusion, (b) leakage through small holes in the cell membrane, and (c) specialised cellular transport mechanism.

The process of diffusion does not depend only on the drug concentration, but physical properties of the substance, lipid solubility and degree of ionisation are also important factors in cellular transport. Drugs with more lipid solubility and less ionisation, diffuse more readily into the interior of the cell.

Penetration of drugs in the C.N.S., aqueous humor and foetal circulation presents special problems as the entry of drugs at these sites is guarded by barriers, the so-called (a) *blood-brain*, (b) *blood-aqueous humor*, and (c) *blood placental barriers*.

Blood brain barrier is probably lipoidal in nature as lipid soluble drugs penetrate into it more rapidly. These barriers, because of their selective nature, limit the attainment of effective concentration by certain drugs, while facilitating the passage of others, making the action more selective.

Thiobarbiturate and volatile anaesthetics enter the central nervous system readily because of their high lipid solubility, 5HT, nor adrenaline are unable to cross blood-brain barrier.

Same mechanism of diffusion is believed to be involved in the transport of drugs across the kidney tubules. This specialised mechanism requires energy and it accounts for the transport of many important lipid insoluble substances like glucose across the cell membrane. The transport of ions in kidney tubules is carried out by similar processes with the help of enzymes like ATPase, succinic dehydrogenase, carbonic anhydrase, etc. Mercurial diuretics prevent this transport by inhibiting SH enzymes and this accounts for the diuretic action.

The above factors form only a small part of the story of pharmacological activity, since they are merely concerned with the mechanism by which the drug is brought to its site of action.

Dissociation: The degree of dissociation of a drug in the body is also important in drug action. Substances, which dissociate in the body into their component ions,—*cations and anions*, are called *electrolytes*. The action of a drug may be exerted in the form of salt or as cations and anions. Further, the extent of dissociation also determines the effective concentration of a drug, already discussed.

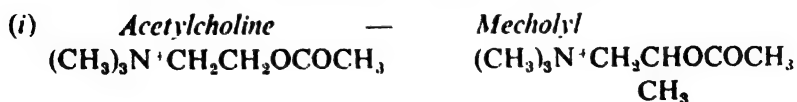
Chemical Constitution: The pharmacological action of a drug often depends upon its chemical structure. The study of structure-action relationship has led to the synthesis of many new valuable drugs. This study not only refers to structural similarity in its broadest sense but also encompasses the more complicated problems of *sterioisomerism*, *spatial configuration* and *molecular orientation*, etc. Though it can logically be conceived that substances with similar chemical constitution, should produce identical actions, but this conception does not work in the domain of biology as an axiomatic truth in every case.

The importance of structure in the activity of compounds was observed for the first time by Crum-Brown and Fraser in 1885, during their studies on alkaloids. They observed that atropine, strychnine and quinine acquired a new property of muscle relaxation on quaternisation, comparable to curare, which itself is a quaternary compound. This earmarked the importance of structural groups in the pharmacological activity of drugs. The following are some of the instances in which, a link between chemical structure and pharmacological actions has been postulated.

Importance of groups. The effect of individual groups on the physiological action of organic compounds has been studied by altering the structure of drugs of known activity. This may be carried out by (a) introduction of a new group, (b) removal of a group already present, and (c) replacement of a group by other groups.

These changes mean a new reaction between the drug and the cell constituents, new route of detoxication and new mechanisms of action.

(a) *Addition, removal or replacement of alkyl groups :*



Extra methyl group in mecholyl makes it less potent, more stable and devoid of nicotinic action.

(ii) Adrenaline—Noradrenaline

Absence of methyl group in noradrenaline is responsible for its more pressor and less antispasmodic action. It also does not produce tachycardia and hyperglycaemia like adrenaline.

(iii) Morphine — Nalorphine

Morphine has a methyl group at aliphatic nitrogen while Nalorphine contains an alkyl group. This change makes Nalorphine a specific antagonist of morphine.

(iv) Barbituric acid — Barbitone

Addition of alkyl group in barbituric acid makes it physiologically active.

(v) Doriden — Megimide

Presence of different alkyl groups is responsible for sedative action of Doriden and analeptic action of Megimide.

(b) Importance of carboxyl (COOH) group :

Benzene	Benzoic acid
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Benzene is inert while benzoic acid has antiseptic properties.

Position (isomerism): If one functional group is present in a ring at a particular position, capable of withdrawing or repelling electrons, removal of such groups to other positions, hampers the activity.

(i) Salicylic acid	Ortho (active)	Meta (inert)	Para (inert)
(ii) p-aminobenzene sulphonamide (active)		m-aminobenzine. sulphonamide (inactive)	

Optical isomerism: Dextro and laevo compounds differ in pharmacological actions either qualitatively or quantitatively.

- (i) L-adrenaline is 15 times more active than dextro form.
- (ii) D-amphetamine is more active than L-amphetamine.
- (iii) Romilar (D-form) is antitussive, while Levallorphan (L-form) is analgesic.
- (iv) Quinine (L-form) is antimalarial, while Quinidine (D-form) is antiarrhythmic.

Interatomic distance: In some drugs, interatomic distance between

two reactive groups is extremely important for a particular type of action.

- (i) The optimum distance between quaternary nitrogen for curari-mimetic activity is 14.5 \AA .
- (ii) For parasympathomimetic activity, the distance between the carboxyl oxygen and quaternary nitrogen, should be 7.2 \AA .
- (iii) The distance between two functional groups of local anaesthetics, sympatholytics and antihistaminics is approximately 5 \AA .

Spatial Orientation of molecules: Molecules of similar configurations may evoke the same type of qualitative tissue response. In Stilbestrol, the substituent groups may place themselves in space in a manner that its structure resembles the configuration of oestrone and thereby elicit oestrogenic activity.

Estrone

→

Stilbestrol

A similar type of orientation of molecules has been observed in case of analgesic drugs, morphine and methadone also.

The importance of the above factors can be visualised in the following groups of drugs where no relation between structures of drugs and their pharmacological actions is apparent:

- (1) *Similar compounds with opposite properties:*
 - (a) Morphine — Nalorphine
Thebaine
 - (b) Megimide — Doriden
 - (c) Male sex hormones — Female sex hormones
- (2) *Similar compounds having different properties:*
 - (a) Steroid derivatives — bile acid, vit. D and corticosteroids.
 - (b) Procaine and procainamide
- (3) *Dissimilar compounds with similar properties:*
 - (a) Procainamide and quinidine
 - (b) Acetylcholine and pilocarpine
 - (c) Reserpine and chlorpromazine
 - (d) Quinine and mepacrine

MECHANISMS OF DRUG ACTIONS

The fundamental mechanism, by which a drug produces its action, is one of the most fascinating problems in pharmacology. No doubt, in recent decades, great strides have been made for understanding this

intricate mechanism, but there are still many missing links in the comprehensive and integrated knowledge of this subject.

This is due not only to the variable physicochemical nature of drugs working in a chain reaction, which cannot easily be deciphered, but also due to still more variable biophysical factors of the living organism, in which, unlike in physical chemistry, the number of variables may be almost unlimited, working often indirectly, which cannot easily be understood. However, with the knowledge of basic mechanisms of drug action, gained so far, the following important theories have been put forward for explaining actions of known and established drugs.

Physico-Chemical Actions: There are some drugs, actions of which can be easily explained by simple physical laws and chemical reactions.

- (a) Bland fixed oils act in a mechanical manner and produce their emollient effects.
- (b) Liquid paraffin, taken by mouth, acts as a lubricating agent.
- (c) Bismuth salts form a protective layer on the mucous membrane and act as gastric sedatives.
- (d) Magnesium trisilicate, kaolin and charcoal produce their action by the process of adsorption.
- (e) Saline purgatives act by osmosis, thus drawing water and stimulating peristalsis.
- (f) Antacids like Sodium bicarbonate or magnesium oxide act by chemical neutralisation of acidity in the stomach.
- (g) Citrates and oxalates act as anticoagulant by removing calcium from blood.

The above reactions do not usually involve any intricate cellular mechanism and occur either superficially and mechanically or extracellularly.

Salt and Ionic Actions : These are also concerned in producing drug action.

- (a) When a dissociable substance is introduced into the body it splits itself into its *ions* and act as (i) Cation, or (ii) Anion.
- (b) When the substance is not dissociated or its basic and acidic radicles produce the same type of action, that is known as '*Salt Action*'.
- (c) When a potent substance like strychnine-SO₄ is introduced, the base being all powerful produces its action. The SO₄ molecule only adds to the solubility. The same is the case with FeSO₄.

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(d) But when NaCl or MgSO_4 is given they act mostly as salts and in case of the latter, both Mg and SO_4 ions are pharmacologically active, producing the purgative action. These are examples of salt action.

(e) Drug which do not dissociate in the body act as molecules, KCN is a poison because the CN ion is dissociable. Potassium ferrocyanide, on the other hand, is not a poison because it acts as a molecule and the CN (cyanide) ion does not dissociate in the body.

(f) Similarly, the scale iron preparations are not easily dissociated and, therefore, they are less astringent than other iron preparations. They, therefore, produce less side effects of iron.

BIOCHEMICAL BASIS OF ACTIONS

1. Enzyme Inhibition: With advances in our knowledge of chemistry, it is becoming increasingly evident that many drugs produce their action by inhibiting specific cellular enzymes. This study is now being extended as an important research tool for tracing intricate pattern of catalysed cellular reactions. The study is also permitting an insight into the physiopathological and biochemical basis of diseases.

Drugs may produce their actions by inhibiting the enzyme system in any of the following manner:

(a) *Non-specific enzyme inhibition:* This involves the denaturation of enzyme protein or reaction with certain types of grouping on the enzyme.

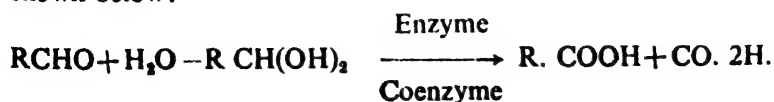
(i) Many antiseptics act by irreversible denaturation of enzyme protein.

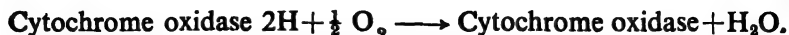
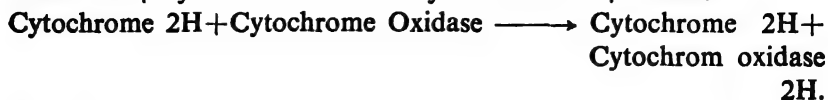
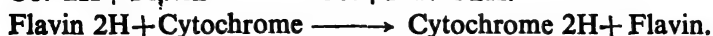
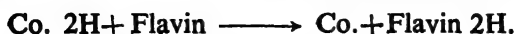
(ii) Trivalent arsenicals and inorganic compounds of mercury combine with thiol group of the enzymes.

(iii) Formaldehyde reacts with the amino group of the enzyme.

In all these cases, a variety of enzymes are affected which have widely differing properties.

(b) *Specific Enzyme Inhibition:* In this case, drugs inhibit enzyme substrate reactions by specifically inactivating a particular enzyme system, either reversibly or irreversibly. The utilisation of oxygen in a cell involves addition of water to a substrate to form a hydrate, followed by dehydrogenation. Reduced coenzyme combines with flavin to form reduced flavin, which is oxidised by cytochrome oxidase and after further reaction with nascent oxygen, water is formed, as shown below:



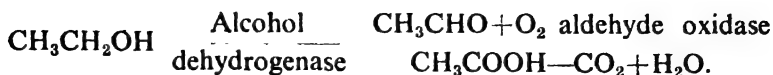


Our present knowledge of drug action on cells indicates that the biological oxidation system in cellular activity is the target of action of many drugs, the cytochromes occupying the centre of aerobic cellular oxidation. The term *glycogenolysis* means a special type of fermentation in which carbohydrate is converted to lactic acid in the absence of oxygen.

Drugs may effect any one of the reactions, mentioned above and thus produce their effects by interfering with cellular respiration, e.g.

- (i) *carbon monoxide* combines with haemoglobin to form carbonyl derivative which does not readily take O_2 . The oxygen transport to the tissues is blocked. Cytochrome system of the cell is deprived of oxygen and so cannot function in a normal manner, leading to cellular hypoxia and depressed cellular activity. Similarly, cyanides specifically inhibit cytochrome oxidase and produce cellular hypoxia.
- (ii) *C.N.S. depressants* like barbiturates and anaesthetics produce their action by attacking at a point between dehydrogenase and cytochrome reductase.
- (iii) *anticholinesterase* group of drugs inhibit the enzyme responsible for hydrolysis of acetylcholine into choline and acetic acid. The enzyme is reversibly inactivated by physostigmine, neostigmine and edrophonium. A number of organo-phosphorous compounds like DFP, TEPP, HETP produce irreversible inhibition of this enzyme.
- (iv) *monoamine oxidase*, responsible for oxidative deamination of a number of biologic amines like adrenaline, noradrenaline, 5-hydroxytryptamine, dopamine and tyramine, is inhibited by a number of drugs. The pharmacological actions of these drugs are produced by the presence of the amines in the system. Antidepressant drugs like iproniazid, nialamide, cyclopropamine, pargyline, produce their central effect through the inhibition of monoamine oxidase and are known as monoamine oxidase inhibitors.
- (v) *antabuse* inhibits aldehyde oxidase in the liver and thus interferes with the oxidation of alcohol into water and carbon-

dioxide at the aldehyde stage, causing a high blood acetaldehyde level.



Accumulation of acetaldehyde in the body makes the patient abhor further drinks and the habit is lost temporarily.

- (vi) *acetazolamide* is a specific inhibitor of carbonic anhydrase, present in renal tubules, C.N.S. and eyes. Inhibition of this enzyme appears to be responsible for diuretic, antiepileptic and antiglaucomatous actions of the drug.
- (vii) *mercurial diuretics* inhibit thiol containing enzymes like succinic dehydrogenase and ATPase, which are responsible for the tubular absorption of sodium. Interference of Na^+ reabsorption thus produced, results in obligatory diuresis.
- (viii) α -methyl dopa prevents the conversion of dopa to dopamine and 5-HTP to 5-HT by inhibiting the corresponding decarboxylases. The hypotensive action of this compound is explained through the blocking of the pathways to the synthesis of noradrenaline and 5-HT.

2. Substrate Competition: A substrate is a metabolic product having a definite chemical configuration which can be absorbed at specific sites on the enzymes for the reaction. A substance closely similar in structure to the substrate can be taken up by the enzyme at the sites, normally occupied by the substrate. The enzyme may not, however, be able to activate the new compound and this causes enzyme inhibition, as the substrate molecules do not have any access at the site of reaction. Such a phenomenon has been designated as *substrate competition* by Gaddum in which the substrate and a chemically closely related drug compete for the active site on the enzyme. The following drugs act by this mechanism.

- (a) Acetylcholine and physostigmine competing for cholinesterase,
- (b) Adrenaline and ephedrine for monoamine oxidase,
- (c) PABA and sulphonamide for the enzyme of folic acid synthesis,
- (d) Vitamin K and dicoumarol for apoenzyme in the synthesis of prothrombin,
- (e) Folic acid and aminopterin for the enzymes of puric acid synthesis.

When a drug competes with another substance present in the body or introduced from outside, for a receptor and the competition between

the two can be explained on the basis of similarity in structure, it is known as *competitive blockade*.

- (a) Acetylcholine and curare competing for the end-plate membrane.
- (b) 5-HT and LSD-25 for the cerebral cortex,
- (c) Morphine and nalorphine for the respiratory centre.

When the competition cannot be explained on the basis of similarity of structure, it is called *competitive antagonism*.

- (a) Acetylcholine and atropine for smooth muscle receptor.
- (b) Adrenaline and sympatholytics for alpha receptors.
- (c) Histamine and antihistaminics for the same receptor.

When a drug competes with the receptor for another drug, it is known as *receptor competition*.

- (a) BAL and sulphydryl enzymes competing for arsenic.
- (b) Physostigmine and cholinesterase for PAM and DAM.

3. Antimetabolite Action: Earlier work of Clark and Ehrlich have brought into light the principle of selective action of drugs which ultimately helped in the development of *specific drugs*. These are the agents which enter into a specific reaction with an essential compound of the organism and make the toxicity selective. Further development of this theory culminated in the work of Woods and Fildes on sulpha drug — PABA reaction in the bacterial cells, based on the principle of biological antagonism.

4. Biological Antagonism: One of the recent approaches in the synthesis of newer drugs is the principle of blocking a biochemical reaction by the use of a synthetic compound similar to the natural metabolite. This consideration has been found to be very fruitful in the development of modern chemotherapy as well as anti-cancer drugs. The process is known as *biological antagonism* and the substance which is structurally similar to the essential metabolite and prevents its utilisation or synthesis, is called *antimetabolite*. Essential metabolites include vital substances like vitamins, hormones, coenzymes, minerals and substrates.

Antimetabolites can be grouped as (a) physiological, (b) chemical, and (c) specific cellular.

(a) *Physiological antagonism:* Controlled balance of normal physiological reactions is due to the antagonism between chemicals in cell processes. If one compound is overactive and shift the normal equilibrium of the system, the antagonistic compounds may balance

this by producing opposite effect. Examples are (i) adrenaline and acetylcholine, (ii) insulin and glucagon (iii) calcium and potassium on heart. These agents oppose each other's action by reacting selectively at different chemical centres in the cell. They are not true antagonists.

(b) *Chemical antagonism*: This refers to chemical reactions between normal metabolites and the drug, producing a compound which is relatively stable, biologically inert or of decreased physiological activity. It includes inhibition of enzymes by drugs and formation of chelates with biologically important metals.

(c) *Specific cellular antimetabolites*: They are defined as compounds sufficiently similar in chemical structures to essential metabolites so as to be able to replace them in biological systems. They lack the activity of the natural metabolites and produce 'conditioned deficiencies'.

Metabolic antagonists can act in 2 ways:

(a) Prevent the utilisation of the metabolites, and

(b) Interfere with their synthesis.

When utilisation is involved, it is called *competitive inhibition*. A constant ratio of inhibitor to metabolite is observed in PABA to sulphonamides. When a small amount of the metabolite is sufficient to overcome any concentration of the inhibitor, it is known as *non-competitive inhibition*, as seen in the cases of thyroxine and thiouracil, and vitamin K and dicoumarol.

Antagonists have been prepared for most of the vitamins and are known as *antivitamins*. Examples are: (a) Thiamine-Pyriethamine, (b) Riboflavin-Galactoflavine, (c) Pyridoxine-Deoxypyridoxine, (d) Nicotinic acid-Pyridine sulphonic acid, (e) Biotin-Desthiobiotin, (f) Folic acid-Aminopterin, (g) Ascorbic acid — Gluco ascorbic acid, (h) Vitamin K — Dicoumarol.

Many synthetic analogues of naturally occurring amino acids have also been found to antagonise the actions of the natural metabolites. Structural analogues of nucleotide moieties such as adenine, guanine, thymine are antagonistic to metabolites in bacterial, viral and neoplastic systems. Amongst the most widely studied purine antagonists are the drugs used in neoplastic diseases. They are 6-diamino, 6-chloro-purine; 6-methylpurine; 2, 6-diamino purine and 8-azaguanine. Similarly for many hormones, substances closely related in chemical structures, which inhibit the synthesis or actions of the hormones have been found. These are: (a) Adrenaline — Alphmethyl dopa, (b) Acetyl choline — Hemicolinium, (c) Thyroxine — Thiouracil, (d) 5-HT — LSD 25, (e) Aldosterone — Spironolactone, (f) Histamine — Antistine.

5. Chelation in drug Action: The action of number of drugs can be partly or wholly explained by their unique properties of forming chelates. Chelation is a chemical process of formation of complexes with metal ions and the compounds which form such complexes, are called chelating agents. Chelate compounds may be formed with ions like iron, cobalt, manganese, magnesium, calcium and copper—all of which are of biological importance and occur in body tissues and fluids.

Chelates are usually coordinated compounds in which, a coordinate bond is formed by sharing of a pair of electrons between an ion or atom of the metal and an ion or atom in the compound. Nitrogen, oxygen and sulphur are the important atoms taking part in this process. A large molecule containing many chelating groups, may be able to form multiple chelate rings. Formation of chelate ring may give newer physical and chemical properties like changes in colour and solubility, increase or decrease in reactivity, stability, reduction in toxicity and even change in optical rotation.

A number of drugs and poisons are believed to act by forming chelate rings with metals for different purposes:

(a) Formation of a chelate for the normal functioning of an enzyme, leading to an antibacterial action:

- (i) 8-Hydroxyquinoline-acting against gram positive organisms forming copper chelate,
- (ii) Oxytetracycline, chlortetracycline-producing their action by the formation of metal chelate complex,
- (iii) Paludrine acting by forming copper chelate.

(b) Formation of a chelate for producing specific actions of drugs:

- (i) Salicylates in rheumatic fever.
- (ii) Thiouracil in thyrotoxicosis.
- (iii) Cortisone in inflammatory conditions.

From the foregoing, it is apparent that cell-drug response which presupposes precise knowledge of drug, as well as of cell at molecular levels, is inevitably complex. A large number of factors—SAR, electronic mobility, charge transfer, interatomic distance, stereoisomerism, affinity and intrinsic activity must all be playing their respective roles and no single factor could explain the nature of drug action. An ideal response, no doubt, would envisage a *fit* between the drug molecule and the components of the complex cell but this riddle cannot be solved till better knowledge of the eventual form in which the drug

molecule, after biotransformation, finally acts on the cell constituents after conformational adaptation. Though we possess much more knowledge of drugs as well as of cells now than before, many important facts are still missing for understanding precise mechanisms of cell-drug interaction. It is, however, known that nature has its own way of dealing with biological phenomena, in which, structure and function from electronic to supramolecular level, may merge into a single unit. But even then, the distinction between structure and function, classic chemical reaction and quantum mechanics at the sub and supramolecular level, will have limited value in the understanding of this complex problem of the nature and mechanism of drug action.

CHAPTER

5

FACTORS MODIFYING DRUG ACTION

Stimulus — DOSE, ROUTE, EFFECT OF COMBINATION AND INCOMPATIBILITY. *Responding System*—AGE, SEX, BODY WEIGHT, PHYSIOLOGICAL STATUS AND CELLULAR RESPONSE

[While considering the various factors that might qualitatively or quantitatively modify drug action, one has to take into consideration the two important aspects, *the stimulus* or the *drug* and the *responding system*, the *patient*, both of which, may be influenced by certain factors—dose, route of administration, drug combination, age, sex, physiological status and special type of cellular response. Methylene blue produces and also cures methaemoglobinaemia in different doses, magnesium sulphate is a purgative on oral administration but an anticonvulsant when given parenterally, children's doses are only a fraction of the adult dose because of their age and body weight, aspirin has little effect on the normal body temperature but may dangerously reduce it in children with hyperpyrexia. Orally, bismuth salts are gastric sedatives but intramuscularly they produce antisyphilitic action. Other factors like acute and chronic accumulation thwarting an immediate or delayed toxic effect, natural and acquired tolerance, tachyphylaxis, hypersensitivity, synergism, antagonism and incompatibility, in which special types of cellular responses leading to lesser or greater degree of reactivity of tissues to particular drugs, also considerably modify drug action. All these factors are to be borne in mind in drug administration to the biological system with finely adjusted interacting steps, as in a chain reaction. The states of development of tissues, pathological conditions and many other factors may often perturb the usual path of reaction in it. The ultimate aim of drug therapy is to cure the disease process with minimum deviations, from the usual reactions of the body, so that maximum good with minimum side-effects, can be produced by the drug during its short sojourn in the body.]

The development of experimental pharmacology has brought into light the rational use of drugs. It has been observed that though majority of human beings react uniformly to any particular drug, some patients behave differently. This reaction refers more often to quantitative than qualitative variations. This matter has been studied in very great details by animal experimentation and it has been well established that diversity is one of the fundamental characteristics of nature and is known as *laws of biological variations*, which may be even of genetic origin.

Age: For obvious reasons, the dose of a drug should vary with the age of the patient because of different body-weight, cellular status and blood volume which last would determine drug concentration. *An adult dose* means the quantity prescribed for a person between

20-60 years of age. *Children* are prescribed a part of the adult dose, which can be calculated from one of the following formulae:

<i>Young's formula</i>	(upto 12 years of age)
	$\frac{\text{Age in years}}{\text{Age in years} + 12} \times \text{Adult Dose}$
<i>Dilling's formula</i>	(Above 12 years)
	$\frac{\text{Age in years}}{20} \times \text{Adult Dose}$
<i>Friend's formula</i>	(Infants under 2 years)
	$\frac{\text{Age in months}}{150} \times \text{Adult Dose}$
<i>Clark's formula</i>	$\frac{\text{Weight in Pounds}}{150} \times \text{Adult Dose}$

The last, calculated according to body weight and the first, according to age, make calculation of dose more scientific.

As a rough guide, a child of 1 year may have 1/13; of 4 yrs. 1/5; of 8 yrs. 2/5; of 16 yrs. 2/3 of the adult dose. Over 60 years, the dosage may slightly be reduced at least for certain drugs like opium, adrenaline, insulin, etc.

As *medullary centres*, more particularly the respiratory and vasomotor, are more sensitive to drug action in children, use of morphine should, as far as possible, be avoided and codeine used instead. Similarly, drugs like aspirin, salicylates, etc. are to be used with caution in children as their "*acid-base*"—equilibrium is unstable. A small dose of aspirin can sometimes produce an exaggerated response in hyperpyrexia and bring down the temperature to an alarmingly low level.

Children, on the other hand, stand certain drugs better and comparatively larger doses of belladonna, digitalis, mercury, antihistaminics and serum than in terms of their body weight, can be given.

In giving drugs to neonates it should be remembered that their drug metabolizing and excretory systems take time to develop.

Sex: Women are considered to be more sensitive to drugs than men. Conditions like menstruation, pregnancy, lactation, which are peculiar to women, should be taken into account while prescribing certain drugs to them. Up to adolescence, they would however stand well the same dose as given to males.

(a) During pregnancy drugs acting on the uterus, drastic purgatives and emenagogues, should be avoided.

- (b) Morphine, chloroform, anthracene purgatives, belladonna would cross placental barrier and affect the foetus.
- (c) Morphine, sulphonamide, hypnotics, belladonna and anthracene purgative, being also excreted in milk, should be given with caution to the nursing mothers.
- (d) Morphine also produces excitatory effects in certain females instead of the usual depressant action.
- (e) Drugs like thalidomide, if consumed as a hypnotic drug during the period of gestation, has been found to produce phocomelia or limb abnormalities in the foetus.

Route of Administration: This factor, connected with absorption and metabolism of drugs, can also influence its action.

- (a) The dose and rapidity of action of a drug vary with the route of administration due to different rates of absorption. That is why the parenteral dose is usually smaller and is used in emergency cases.
- (b) Drugs which are irritating or are destroyed in the G.I.T.—emetine, adrenaline, insulin and several other hormones—are given parenterally.
- (c) Vasoconstrictors are inadequately absorbed from oral and topical routes.

Some drugs also produce different effects when given by different routes, e.g. Magnesium sulphate and Bismuth salts, referred earlier.

Time: Time of administration sometimes modifies the action of a drug. This is especially applicable to oral administrations. Drugs are usually better absorbed when given in empty stomach but certain drugs are better tolerated if given after meals.

- (a) Drugs like iron, codliver oil, antacids are preferably given after meals while insulin S.C. is given before meals to avoid hypoglycaemic action.
- (b) Hypnotics are more effective when given at bed time in the quiet of night.
- (c) Drugs intended for local action on stomach are usually given before meals and saline purgatives act more quickly in empty stomach and are administered early in the morning but slow acting purgatives like senna and aloes are given at night.
- (d) Alcohols are more rapidly absorbed from empty stomach.

Frequency: To produce an optimal effect, a drug should be present in the system in effective concentration. To maintain this, drugs are administered at frequent intervals. The rate of absorption, metabolism and elimination play an important part in regulating the spacing of doses.

Drugs which are rapidly absorbed and rapidly excreted, are to be administered at frequent intervals, e.g. sulphonamides, penicillin and salicylates; while drugs which are slowly eliminated should not be used too frequently for avoiding the danger of cumulation, e.g. digitalis, thyroxin, bromides, heavy metals.

Pathological Conditions: The ability of drugs to produce a differential effect in normal condition and under pathological states is the basis of *drug therapy*.

- (a) Antipyretics produce insignificant effect on normal temperature.
- (b) Diuretics are usually more effective in cases of oedema.
- (c) Ecbolics are more effective on pregnant uterus.
- (d) Diarrhoea may decrease absorption of certain drugs from the gut.
- (e) In myxoedema and cirrhosis of liver usual doses of morphine may be too toxic for the patient.
- (f) Digitalis acts as a diuretic only in patients with congestive cardiac failure.
- (g) Histamine causes a rise in B.P. in phoeochromocytoma while producing a fall in normal prsons.

Climate: Guineapigs show greater sensitiveness to ouabain in winter and colchicine is 400 times more potent in frogs at 30°C than at 19°C.

Mental Condition: A sound inclination of mind towards the action of a drug sometimes enhances its effects. A small dose of hypnotic may be sufficient to induce sleep in them. Similarly, emotional upset may delay the absorption of drugs.

Cumulation: This means accumulation of drug in the body which happens when the rate of excretion is lower than the rate of absorption of a drug. Cumulation may be of different types.

Initial cumulation of rapidly excreting drugs: All drugs have to cumulate initially in the body before an action is produced. This is why drugs are administered in divided doses instead of an initial loading dose for effecting optimal concentration for initiating drug action as that might produce toxic effect in a certain percentage of cases.

Examples:

- (1) Drug x is given 1 gm./4 hourly. Rate of excretion $1/5$ gm./4 hourly. After the first dose, the drug would accumulate to the extent of $4/5$ gm. in the body and this would continue till 5 gms. of the drug are in the body, after which, the rate of absorption and excretion will equalise.

(Total Drug = 5 gm; rate of excretion = $1/5$ th or 1 gm. drug left = 4 gm. After next dose of 1 gm. total drug again 5 gm; so on so forth).

- (2) Sodium Salicylate—*Dose:* 1 gm./4 hourly. Rate of clearance = $1/10$ th gm./4 hourly.

The drug will accumulate to the extent of 10 gm., after which, absorption and excretion being equalised, there will be no further accumulation provided that the dose or the interval for repetition of dose is not altered.

Cumulation of slowly excreting drugs, e.g. digitalis, thyroxine, etc.

Dose of Digitalis Tincture, 1 ml. at a time/day. Clearance $1/14$ ml./day. The drug will accumulate upto a total of 14 ml. in the body. thereafter no further cumulation, if the dose is not altered. Hence greater initial dose prescribed in intensive digitalis therapy.

Cumulative Poisons: These are generally heavy metals like arsenic, lead, etc. which accumulate even in trace doses and are not recommended for any prolonged use.

Delayed action: (a) Radium, X-rays, sometimes even one single exposure producing tumours after years. (b) The plant—*Senecio latifolia*, after one feed in cattle producing liver cirrhosis after a latent period of months. This may be the after effect of a series of biochemical reactions taking place in the liver.

Thus the Law of Cumulation is dependent on: (a) dosage and rate of absorption and (b) rate of excretion. Its accurate knowledge enables us to effect (a) rapid action by giving an initial loading dose, and (b) no toxic effect because of subsequent maintenance doses.

Tolerance: It is an unusual phenomenon of resistance to the action of an ordinary dose of a drug shown by certain individuals. Two types of tolerance are generally seen.

- (i) *Acquired tolerance* is produced by continuous use of a drug for a prolonged period like morphine, aspirin and barbiturate.
- (ii) *Natural or congenital tolerance:* It is exhibited in a race since birth.

Acquired tolerance depends on the following 4 factors:

- (a) *Poor absorption*: The drug may be poorly absorbed from the G. I. Tract and excreted before the required optimal concentration for response is attained. This is a *pseudo tolerance*, as the specific cells on which the drug acts are not involved, e.g. chronic alcoholics sometimes do not absorb the entire quantity of alcohol because of chronic gastritis.
- (b) *Quick excretion*: Ingestion of bromide along with sodium chloride enhances the excretion of the former in urine. This is pseudotolerance.
- (c) *Rapid detoxification*: Tissue cells may be capable of rapidly detoxifying drugs, e.g. rapid oxidation of aliphatic side chains of barbiturates by liver cells. This capacity may be congenital or acquired and is looked upon as *true tolerance*.
- (d) *Cellular acclimatisation*: The tissue cells are acclimatised or adopted to the presence of the drug and do not respond to an ordinary concentration. This is *true tolerance* and is due to the production of a type of *tissue immunity*, e.g. alcohol, tobacco and opium. In case of opium, cells of the C.N.S. are specifically involved without any effect on the pupil and the G.I.T. This form of cellular adaptation is based upon some biochemical transformation without detectable structural changes. It is said that the enzyme which demethylate morphine and the receptors for its action are closely related. Repeated use of the drug inactivates the enzyme and the receptors. Non-availability of the specific receptors is responsible for the decrease in response. This phenomenon may be only a temporary one as is seen in cases of glyceryl trinitrate.

Tolerance to a drug is soon lost on discontinuation for some time.

Cross tolerance: The prolonged use of one drug may induce tolerance for others of the same or different groups.

- (a) A patient tolerant to one barbiturate is tolerant to others also.
- (b) Chronic alcoholics are tolerant to anaesthetic action of ether and barbiturates.

This may be due to the actions of these drugs on the common receptors which are subsequently blocked.

Natural or Racial tolerance: Racial and natural or congenital tolerances are seen in human beings as well as in animals and may be of genetic origin.

- (a) Negroes are more tolerant to the mydriatic action of ephedrine.
- (b) Eskimos can tolerate large quantities of fat diet and their tolerance for carbohydrate seems to resemble that of diabetics.
- (c) Rabbits tolerate larger amounts of belladonna because of the presence of atropinase in their blood.
- (d) Invertebrates tolerate larger doses of strychnine as they lack spinal cord on which the drug mainly acts.

Tachyphylaxis: This is a quickly developed but short lived resistance to the action of drugs due to the repeated administration of the same dose within a short time. Classical example is that of ephedrine which produces rise in B.P. in dogs. Subsequent doses produce less and less rise till a dose may not produce any rise at all. It differs from tolerance in: (a) rapid development, and (b) original effect not returned even in high doses as seen in tolerance. It is probably due to a transient saturation of the cell receptors with the drug, subsequent doses producing less effect because the receptors remain engaged and cannot be activated. This phenomenon has also been seen in case of tyramine and phenelzine.

Idiosyncrasy: It is an extraordinary and unusual type of cellular response to a drug which is different from its usual pharmacological action. The possibility of these abnormal drug reactions should be carefully noted during drug therapy.

- (a) Morphine can cause excitement in some cases rather than sedation.
- (b) Quinine may produce ringing in ears even in smallest possible doses.
- (c) Hyoscine, a sedative, may cause hallucination.
- (d) Acetylsalicylic acid, arsenic compounds, sulphonamides and penicillin are known for this reaction. Mechanism of idiosyncrasy is still little understood.

Hypersensitivity: Of late, instances of drug sensitivity are increasing. It is one of the most serious problems in drug therapy and certain drugs like penicillin, which usually are known to have very low toxicity, are now producing very serious reactions and even death.

A simple drug like aspirin after combining with body protein can cause hypersensitivity or drug allergy. These reactions, if produced immediately, with fall of B.P. are known as "*anaphylactic shock*" and if delayed, it is then taken as simple "*allergic type*". Both the types are, however, due to "*antigen — antibody reactions*", releasing histamine

or other active substances from the tissues. This type of reaction also occurs with certain drugs which, besides producing their usual actions, produce anaphylactic or allergic reactions. *Serum sickness*, penicillin anaphylaxis are some of the serious problems of the day.

In drug allergy, the manifestations produced by the different drugs are identical and do not depend on the nature of the drug: Thus, aspirin, insulin, streptomycin, though differing in nature, will cause allergic reactions of the same type.

Biochemical and Emotional Individuality: From the analysis of biological variations, it is now apparent that subtle biochemical deviations in an individual might ultimately be responsible for some of the variations. This accounts for modification of drug action and response in different individuals. Similarly, the psychogenic individuality also cannot be ignored. This can be easily associated with the exaggerated or substandard response to drugs, which stimulate or depress the C.N.S. and acting on higher centres, produces subjective responses. The varying responses of different individual to sedative, hypnotics, tranquilisers and placebos, could thus be accounted for because of different psychological make up of certain individuals.

Physical Dependence: Prolonged use of drugs like morphine, alcohol and bromides causes changes in the physiological processes, resulting in an altered physiological state. For maintaining the normal function, the presence of the drug is quite essential. Sudden withdrawal of the drug leads to serious disturbances in the functions and may induce abnormal reactions, called the '*withdrawal symptoms*'.

Addiction: It is a form of chronic intoxication from certain habit forming drugs producing a sense of well-being, craving and loss of self-control. He soon develops dependence and has to get it at any cost, by any means and from any source and use it in gradually increasing doses for getting the same effect. Addiction does not occur with all drugs. C.N.S. depressants like morphine, pethidine, methadine, heroine, cocaine, alcohol, tobacco, charas, barbiturates, bromides are the common substances known for this physical and mental evil. Development of addiction depends on psychic and physical dependence as well as tolerance. This will be further discussed in a later chapter.

Drug Resistance: Development of tolerance by certain organisms to drugs administered repeatedly to the host probably in inadequate doses, is known as drug resistance. Improper use of potent chemo-

therapeutic and antibiotic drugs has been partly responsible for the development of this new problem. The mechanisms of drug resistance may be due to emergence of drug resistant organisms by natural selection or by heredity, developments of alternative metabolic pathways in the organisms or enhanced destruction of the drug (penicillin by penicillinase).

Some microorganisms develop alternative metabolic pathways for their growth and maintenance. A drug forms the part of these biochemical processes so that the metabolism now becomes dependent on the presence of the particular drug. This phenomenon in organism is popularly known as *drug dependence*. A familiar example of this is the dependences of *E. coli* on streptomycin.

Drug Combination: Two or more drugs, when simultaneously administered, can enhance or retard the action of one another. It is also likely that in these combinations, the action of either drug is not altered, but the effectiveness is changed. Such combinations are commonly referred to as *synergism*, and *antagonism*.

Synergism: If two or more drugs, having similar actions, when administered together, produce an effect greater than their individual effect, but not more than the sum of individual action, the resultant action is called as additive *synergism* or *summation* effects. This accounts for why more than one ingredients are usually prescribed. Such combination of drugs is believed to produce therapeutic effects with a smaller dose of each and there is a greater margin of safety due to lesser chance of individual toxic effects, which is not always true.

- (a) Half dose of potassium bromide and half dose of chloral hydrate produce the full hypnotic effect.
- (b) Ether and chloroform produce synergistic effect.
- (c) A case of insomnia due to muscular pain, responds better to a combination of aspirin and lumunol than to lumunol alone.

Potentiation: When the combined action of two or more drugs is more than the sum of individual effects, and is probably a multiplication factor, it is called '*potentiation*'.

- (a) The administration of mercurial diuretics preceded by ammonium chloride produces much greater diuresis than what could be accounted for from their individual action.
- (b) Combination of ephedrine and adrenaline act as a better bronchodilator.
- (c) Phenolphthalein which acts on the small intestine, synergises with cascara, which acts on the colon.

- (d) Cocaine, followed by adrenaline, produces greater rise in B.P.
- (e) Eserine potentiates the action of acetylcholine.

Antagonism: When two or more drugs are combined together to counteract the side or undesirable effects of one by the other, it is known as drug *antagonism*. This is considered to be useful in cases of treatment of poisoning. The antagonism is brought about in three ways:

- (a) *Chemical Antagonism:* Two drugs react chemically and neutralise each other's action forming an inert compound. This is the basis of treatment of certain poisons.
 - (i) Acids for alkalies and vice versa.
 - (ii) BAL for metals like arsenic, mercury.
- (b) *Physiological Antagonism:* In this case, drugs produce opposite effects without reacting with each other. The site of this antagonism may be the same or different structures.

Same Structure

- (i) Barium and papaverine on small intestine.
- (ii) Analeptic and barbiturates on C.N.S.
- (iii) Barbiturates and bemegride on the respiratory centre.
- (iv) Calcium and potassium on heart.
- (v) Ach and atropine on cholinergic receptors.

Different Structure

- (i) Adrenaline and nitrites on B.P.
- (ii) Adrenaline and histamine on bronchial muscles.
- (iii) Adrenaline and acetylcholine on the intestine.
- (c) *Biological Antagonism:* In this form of antagonism, a drug competes with another, having chemical similarity for the same cell receptors. It interferes in the interaction of natural metabolites or the substrates with the receptors. It is also called substrate competition or competitive inhibition as referred to earlier.
 - (i) Morphine and Nalorphine on the respiratory centre.
 - (ii) Histamine and antihistaminic drugs.
 - (iii) Folic acid and Aminopterin.

The doses, time and route of administration of each antagonist determines the overall effect, which cannot always be predicted.

Incompatibility: When two or more drugs cannot be prescribed together because they do not get along well, they are known as incompatibles. Incompatibility is of 3 types: (a) physiological or therapeutic; (b) physical; (c) chemical.

Physiological: When one drug opposes the action of the other, it is known as physiological incompatibility, e.g. caffeine and barbiturates, the former being a stimulant and the latter a depressant of the C.N.S.

Physical or Pharmaceutical Incompatibility: It may include molecular change, insolubility or immiscibility, e.g.

- (a) oil and water are not miscible.
- (b) water and resinous matter form precipitate.
- (c) Camphor, menthol and thymol when rubbed together, undergo liquefaction.

Chemical Incompatibility: This is due to chemical reactions of various ingredients in a prescription.

A. Intentional: When this interaction is desired by the physician for the benefit of the patient, e.g. *Seidlitz* powder. When sodium bicarbonate and tartaric acid are mixed, CO_2 is liberated and the effervescing fluid acts as a soothing carminative.

B. Unintentional due to the ignorance or inadvertence of the prescriber.

- (a) Acids + Alkalies = neutralisation.
- (b) Alkaloidal salts + alkalies or tannic acid or heavy metals = precipitation.
- (c) Sodium salicylate + acid = precipitation of salicylic acid, an irritant.
- (d) Iron preparation + salicylate or benzoate or tannates = change of colour and precipitation.
- (e) Potassium chlorate + glycerine = explosion.

Every physician is required to study drug incompatibility carefully and prescribe drugs, avoiding its occurrence, excepting in cases of intentional ones.

The above are some of the general and prevailing concepts with regard to the modification of drug action by various factors, including drug combination and interaction. However, with the recent advances in cellular and biochemical pharmacology, thanks to the discovery of potent therapeutic and other drugs, it now appears that the problem is not so simple as conceived so far. It is a known fact that in drug combinations, as in the cases of sulphatriad and general anaesthetic agents, there are many pitfalls in the achievement of predictable

actions. Similarly, drug combination and drug interaction in the cases of simultaneous use of digitalis and thiazide diuretic, is not free from undesirable outcomes. This in fact is to be expected where we conceive of the complex nature of the drug action as discussed in the previous chapter, in which, the molecular aspect of drug response on cells has been indicated. The way modern concepts of drug action at cellular level is advancing, one is oriented to think that one drug for one condition, at one time, should be all that one could consider, till further work on drug interaction has been carried out.

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Plate VI

THEY PAVED THE PATH OF QUANTITATIVE PHARMACOLOGY AND DISCOVERY OF SPECIFIC THERAPY



FIG. 20. *A. J. Clark*. A pioneer worker in fundamental pharmacology whose penetrating concepts on the mode of actions of drugs on cells have brought cellular and quantitative pharmacology and specificity of action into existence.



FIG. 21. *H. H. Dale*. An eminent scientist of the present era whose work covers a very wide field—vasomotor reversal, histamine, cholinergic transmission, etc. A mastermind of the century in physiology and pharmacology alike.



FIG. 22. *J. H. Burn*. An outstanding worker on acetylcholine, local hormones and also on bioassay of drugs.



FIG. 23. *J. Gaddum*. Worked on many biologically active 'substances, mechanism of drug action and biometry. The concept of 'substrate competition' emanates from him.

Plate VII



FIG. 24. Some of the important participants of the First International Meeting
on Biological Standardisation at Geneva

SECTION

II

BIOASSAY AND GENETIC PHARMACOLOGY

CHAPTER

6

EVALUATION AND ASSAY OF DRUG

DEFINITION, GENERAL PRINCIPLES. STANDARDS, TYPES AND METHODS OF ASSAY. BIOLOGICAL VARIATION, BIOMETRY AND STATISTICAL ANALYSIS OF DATA. INDIVIDUAL ASSAY METHODS.

[These two terms—'Evaluation and bioassay', are not synonymous in Pharmacology. While evaluation refers to the study of a drug from all aspects, with a view to assess its value and further possibilities for clinical use, the word assay means testing of a sample in terms of an accepted standard, in respect of purity, potency and toxicity.]

Evaluation of any new drug is carried out by chemical and pharmacodynamic studies in the drugs research laboratory, inclusive of toxicity studies and clinical trials in the hospital. In the *bioassay* of a drug, the important and almost unsurmountable hazard is the *biological variation* which is minimised by planning of experiments, its sizes, sex, litter and weight distribution in the groups of ST and T identically. Various types of assay methods are also selected for obtaining dependable and comparable results. Cross-over and 4 point tests also minimize the errors. For this work, statistical methods with appropriate dose-response curve, SD, SE of the mean, significance of a difference, determination of Fiducial limit and probability of error are also helpful for minimizing the experimental error. However, the variability which is probably a genetic factor cannot be completely eliminated but only reduced within a workable limit.

Of the 2 methods of assay, *chemical* and *biological*, the former is a measure of purity and therefrom potency by simpler methods and applicable to drugs of known chemical entity, while the latter which is a measure of potency directly and thereby its purity, by time consuming experimental procedures, giving place to the first when the substance is chemically identified and an accurate assay method is developed.]

EVALUATION OF A NEW DRUG

The discovery of a new drug and the correct assessment of its real therapeutic value involve very elaborate studies by a team of workers comprising organic and pharmaceutical chemists, botanist, biochemist, bacteriologist, pharmacologist, toxicologist, clinician and statistician.

Chemical Study: This, in fact, is the first and the most important step in the discovery of any new drug. Depending on the exact source of the substance, vegetable, animal or synthetic, the prospective drug has to be obtained in the pure and active form. In case of a vegetable drug, the plant has to be phytochemically analysed, the active principle carefully isolated by chemical and chromatographic analysis and its exact chemical nature established. The biological substances are to be obtained in purified, active forms after elimination of unwanted proteinaceous and other substances liable to produce toxic reactions. In case of synthetic compounds, the main problem is the manufacture of a very large series of compounds and derivatives to be able to get one with desired effect. In this way, a new drug, in a suitable dosage form, soluble in water or a suitable solvent for biological studies, is prepared for further evaluation.

Pharmacodynamic Study: At this stage, drug evaluation constitutes a tactical problem encompassing some of the following techniques:

(a) Study of effects of the new drug in unicellular organisms like amoeba and paramacium

(b) Detailed studies on isolated and in situ organs for ascertaining its actions on various systems, C.N.S., C.V.S., G.I.T., genito-urinary and respiratory systems, etc.

(c) In collaboration with biochemists, studies on blood chemistry, metabolism, endocrine functions and route of administration are undertaken.

(d) By a series of carefully planned experiments, study of site and mode of action of the drug by biochemical and physiological techniques, involving even isotopic study, with a view to follow the course of the drug in various systems and its biotransformation.

(e) Finally, *therapeutic efficiency* is tested in suitable animals after experimental production of conditions resembling clinical diseases and the *therapeutic index* or *margin of safety* carefully worked out for minimizing the hazard of toxicity in human patients. Study of acute, subacute and remote toxicities, involving even genetic changes, are investigated in close cooperation with the pathologists, bacteriologist and biochemists.

(f) After ensuring the suitability of the new drug in all these respects, it is passed on for controlled *pilot* and *large scale clinical trials* on human beings.

Clinical Trial: It is not possible to predict the effects of a new drug in human beings from the results obtained in lower animals. It is,

therefore, necessary to evaluate the drug in human subjects and the procedure involved, is known as *clinical trial* which is carried out in four steps:

Step I: (a) Main problem in the initial human studies is to find out the first dose to be used. This is determined as follows: On the basis of acute animal toxicity studies, increasing doses of the agent are given to selected animals to obtain *minimum effective dose* (M.E.D.) The initial human dose will be a fraction of this M.E.D. — 1/200th or 1/10th depending on the species of animal used, using the same route of administration. (b) The calculated initial dose is then given in one or two healthy human beings to start with and if no response, it is gradually increased till drug activity appears. This is the M.E.D. which is given to several individuals with a view to find out if the action is reproducible.

Step II: (c) Effect of drug after acute and subacute administration to human volunteers to determine tolerance, therapeutic range, average dose, side effects and indications of toxicity. The effect of drug is evaluated from a *base line*, prepared in advance by careful observation of each person, including physical examination, body weight, pulse, B.P., urine analysis, E.C.G. and other studies. (d) If no serious toxicity is detected, the drug is given to a small group of patients with a specific disease under controlled conditions. Allocation of the patient to the drug treated group may be at random, or based on certain criteria, like age, sex, body weight, stage of the disease, etc. (e) When evaluation of a drug involves personal judgement, e.g. analgesic or sedative activity, additional controls are used to avoid introduction of bias. This is achieved by *single blind* (physician and associates but not the patient, know the substance being used) or *double blind* (neither the associates nor the patient know the identity of the substance) trials. All materials are coded and the trial includes test substance, a placebo and a standard of reference. A placebo reactor is thus eliminated from the trial. (f) Side by side, haematologic, hepatic and renal function tests are carried out for evidence of drug toxicity.

Step III: (g) When the safety of the drug is adequately established, it is tried on a larger number of patients to determine safety, effectiveness and optimum dosage of the drug.

Step IV: (h) After it is proved from these studies that the drug is safe and effective, it is passed on to general practitioner for the last and the most decisive evaluation. If the drug is found in order, it is first included in New and Non-official Remedies and after more extensive clinical assessment for a period of 5-10 years, it acquires a more official status by being included in official pharmacopoeias.

From the results obtained by these workers, the fate of a new drug may be: (i) enthusiastic reception, (ii) qualified use, (iii) declining use due to ineffectiveness, side effects, late toxicity, etc., and (iv) obsolescence.

It is thus evident that discovery of a new drug, inspite of a very elaborate systematic study, is still a chance observation, as all discoveries are. This is evident from compounds like 914, 606, 13099, in which the last compound was found to be promising after discarding all the others in the series. Therefore, no doubt, there is an element of chance in all outstanding discoveries but it should not be forgotten that "Chance also favours a mind that is receptive."

ASSAY OF DRUGS

Two centuries ago, Voltaire defined Medicine as the "Art of pouring of drugs, of which one knew little, unto patients, of whom the doctor knew less."

This ancient sneer, though exaggerated, clearly indicates that in the management of diseases, there are at least two important variables,—the patient and the drug.

Variability and variation are natural phenomena seen in all living organisms. They can be minimised by careful experimentation, but not eliminated altogether, e.g. (a) At the end of a class, the pulse rate of a group of healthy students was found to be varying from 52-103 and systolic blood pressure from 85-184 mm. Hg. (Alvarez). (b) The narcotic I.V. dose of sodium amytal in labour cases, was found to be ranging from 5-10 mgm./kgm. (Paxson) and similarly, sodium salicylate was found to produce toxic symptoms in doses ranging from 40-270 grs. (Hanzlik).

The above examples indicate the range of biological variations, and since the patients cannot be standardised, the only alternative is to standardise the drugs. This is why B.P. and I.P. prescribes a dose-range, instead of a single, fixed official dose for a drug.

Correct evaluation of a drug presupposes. (i) purity, (ii) potency and (iii) keeping qualities for the determination of which chemical and/or biological assays are essential.

CHEMICAL ASSAY

Chemical testing of pharmaceutical preparations refers to the estimation of (a) active principles — alkaloids, glycosides and other consti-

tuments, having tests for assessment, (b) spirit strength, (c) total solids, (d) ash value, (e) iodine value, (f) saponification value, etc.

Through these chemical tests identity and purity of a drug are determined and purity is considered to be an index of potency.

TABLE
A LIST OF IMPORTANT DRUGS ASSAYED
BY CHEMICAL METHODS

Acids, Alkalies & other Chemicals,	
Salicylates, Vitamin C, Isoniazid,	
Ferrous sulphate	Titrimetric Method
Phenobarbitone, Santonin, DOCA	Gravimetric Method
Vitamin A, B ₁₂ , Reserpine, } Nalorphine, Acetazolamide }	{ Spectrophotometric Method
Riboflavin, Thiamine	Fluorophotometric Method
Pepsin, Pancreatin, Malt Extract	Enzymatic Method
Belladonna, Ipecac, Opium, Nux vomica	Different Alkaloidal Assay Methods
Nitrites, Gas anaesthetics	Gasometric Method

With advances in our knowledge of drug chemistry, chemical tests which are simpler, more accurate and less cumbersome are gradually replacing the biological assays. The latter being a measure of activity and toxicity, has however, more direct bearing in drug therapies.

BIOLOGICAL ASSAY

Bioassay measures the potency and concentration of drugs through one of their principal pharmacological effects on living animals or tissues. It also sometimes acts as a tool for research by providing a rough and ready guide, regarding the presence of some unknown substances. Being an accurate measure of activity, it has brought into being the concept of 'Quantitative Pharmacology' in drug action.

In the earlier days, no accurate units of measurement existed. That is why we still come across the foot, yard, palm, digit, handful, table spoonful, Winchester quart units, as rough and ready measures. The pharmacologists, who are familiar with the laws of biological variations with reference to drug action, know too well the accuracy of such '*king units*', "if they have to consider the different king units from Victor Emanuel, Kaiser, Napoleon, Louis XIV..."

It was, therefore, necessary to formulate standards for uniform assessment of values and after World War I through the League of Nations and Narcotic Sections, International Standards and Bioassay

of Drugs Sections, were introduced, with a view to prepare and supply drugs of uniform quality and potency, all over the world. This Biological Section, through its selected committees of scientist delegates of each country, was assigned the duties of evolving methods of drug testing and standards and drug policies and establish international standards for comparison, acceptable to all the countries.

Standards and Units: These are accepted preparations of international standards in stable forms, representing fixed units of activity per unit of drug, as accepted and recommended by the Expert Committee of W.H.O. for the testing of commercial samples of drugs.

There are 32 of these, prepared with the help of recognised laboratories of various countries and stored in National Institute for Medical Research, London, and State Serum Institute, Copenhagen.

In India, subsidiary standards are kept in *Central Drug Laboratory*, Calcutta. They are not only prepared and stored under standard conditions, but are used as International Standards all over the world. The ampoules are nitrogen filled.

TABLE
SOME OF THE INTERNATIONAL STANDARDS

National Institute for Medical Research, London	<i>Vitamins</i> —A, B, C, D, E	State Serum Institution, Copenhagen	<i>Antitoxins</i> —Diphtheria, Tetanus, Staphylo, Gas gangrene
	<i>Hormones</i> —Insulin, Post. Pituitary powder, Oestradiol		
	Progesterone, Androsterone, Gonadotrophin,		<i>Sera</i> —Antidysenteric, Anti-pneumo coccal
	Thyrotrophin		
	<i>Others</i> —Digitalis, Neoarsphenamine, Penicillin, Heparin		<i>Others</i> —Old tuberculin

Principles of Bioassay: (a) The basic principle is to compare the test substance with an international standard preparation of the same, to find out, how much of the test substance is required to produce the same biological effect as the standard. Reference standard must owe its activity to the same active principle for which the sample is being assayed. (b) Bioassay usually utilises a recognised action of a drug, but if the method of assay tests the important therapeutic constituents, it is not necessary that the procedure be related to therapeutic effects only. The activity assayed, however, must be the activity used therapeutically, e.g. assay of ergot alkaloids by cock-comb method. (c) The

problem of biological variation must be minimised by proper selection of animals and use of adequate number of test objects.

Types of Bioassays

(a) *Direct assays* depending on effective dose in each animal. A comparison between the average results of the two groups of animals gives satisfactory results, e.g. end-point determined in guineapigs or cats in digitalis assay.

(b) *Assays depending on measured effects*. In these, the effect of a drug is measured on whole animals or isolated tissues, e.g. vitamin D and thyroid assay.

(c) *Quantal effects* depending on the percentage of animals showing some definite positive reaction like death, oestrus or hypoglycemia. In case of the first, all or none phenomenon, i.e. *death* or *no death* is taken into consideration.

(d) *Microbiological assays* depending on inhibitory effects of drugs on microorganisms, e.g. assay of penicillin.

Factors Influencing Bioassay: Major factor influencing bioassay is *biological variation*. It is important to cut down this as much as possible by :

(a) *Planning of experiments:* (i) selection of animals, due consideration being given to age, sex, body-weight and litter; (ii) use of sufficient number of animals, (iii) conducting assays under standard laboratory conditions and (iv) proper distribution of animals in different groups.

(b) *Cross-over test:* Wherever possible, a cross-over test is carried out so that each animal receives both the standard and the test substance, in succession.

Planning of Experiments : This involves (a) selection of animals, (b) size and experimental number of animals, (c) conduction of assay under standard conditions for obtaining significant results by minimising biological variations.

Selection of animals is carried out on the basis of their suitability for a particular assay, e.g.

- (a) Mice and rats — toxicity tests,
- (b) Guineapigs — pituitrine assay,
- (c) Cats — digitalis and adrenaline tests,
- (d) Monkeys — antimalarials.

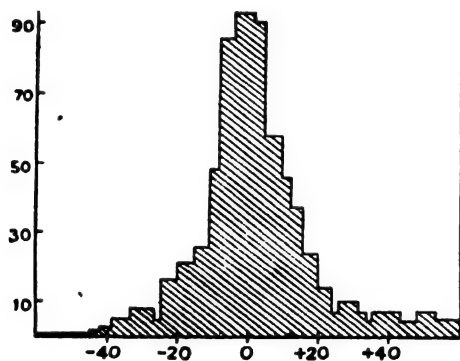
Any and every animal is not suitable for all assays, e.g. the frog method of digitalis assay is much less accurate than the cat method.

To further reduce the variations, animals from same litters of same age, weight and sex equivalent are used and same laboratory diet and experimental conditions are maintained in each case.

Fairly large number of animals are to be used for each estimation. For working out the dose-response curve with the international standard 30-100 animals for each dose and for testing of samples 6-30 animals for each series of experiments, are to be used.

All this is due to the fact that the major factor influencing Bioassay is the *biological variation* which is almost intrinsic in all biological responses to the extent that no two individuals, not even the twins, always respond to a particular drug in an absolutely identical manner. This is evident from any bioassay work, whether that refers to the *toxicity* or *therapeutic efficiency* tests.

For example, Burn working on the *lethal dose* of *digitalis* on cats, observed individual figures like 75, 92, 126 and Wizingardner, detailing these experiments on 573 cats, observed the distribution of variation, as detailed in Fig. (a).



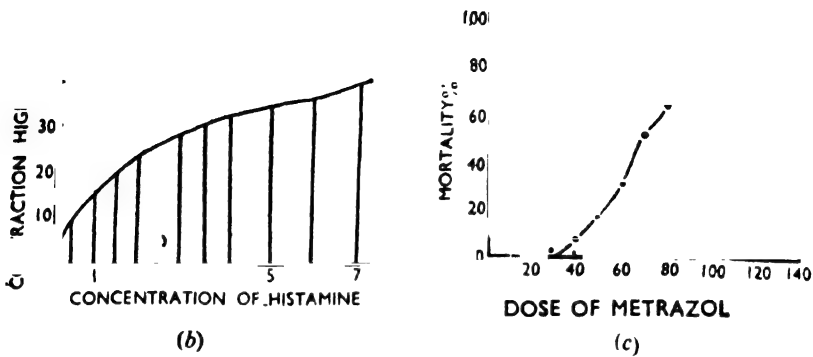
(a)

Distribution of Variations around the Mean

Statistical Methods: For any accurate work, it is necessary to determine the following:

- (a) A 'dose-response curve' on a large number of animals and working out LD_{50} , in case of toxicity tests. The shape of the curve depends on the type of response utilised, *hyperbolic*,

when the response is graded, while *sigmoid*, if the response is quantal—Figs. (b) & (c).

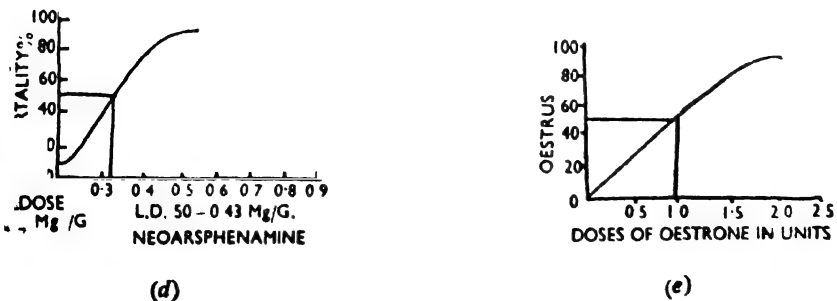


- (b) Scatter of observations referring to the mean and also standard deviation and standard error of the mean.
- (c) The significance of any difference observed.
- (d) Binomial distribution or chance of death and probability of error.

Dose-Response Curve: This actually refers to the response observed in a particular group of experiments to graded doses of known or unknown drug, for comparison.

For working out the same, at first, effect of a minimum and maximum dose is determined; this is then increased and reduced with the specific purpose of what minimum dose will just produce the effect, and what minimum dose will produce the maximum effect. The former is called MED and the latter MTD. In case of toxicity, they are known as LD_0 and LD_{100} respectively.

Having determined this, the range is divided into graded doses either in arithmetic or logarithmic scales and the dose response curve, as shown in Figs. (d) & (e).



The dose-response of different drugs vary a lot, but they are of the same pattern for any species of animals used.

Obviously more accurate work can be done with arsenicals than oestrone, as animals can discriminate better and slight variation in dosage at the level of LD_{50} is reflected better on effect than in the case of oestrone.

The above is the usual method of working out the dose-response with a large number of animals, but if fairly dependable curve is desired with comparatively less number of animals, the following method can be used.

Karber's Method: Some of the observations obtained by the author with urea stibamine are shown in the Table.

TABLE

<i>Log dose</i>	<i>Mg./Kg.</i>	<i>Observed mortality</i>
2.10	125.9	0/8
2.10	141.3	1/6
2.20	158.5	3/6
2.30	199.5	1/6
2.40	251.2	4/6
2.50	316.2	6/6

LD_{50} is then worked out with the help of the following equation,

$$\text{Log } LD_{50} = X_0 - E \frac{(n1 + n2)d}{2} \text{ where } X_0 = \text{Log dose of } LD_{100},$$

p^1 and p^2 = Log doses of 2 successive pairs of observations, d = Log of difference between p^1 and p^2 .

In this particular case, $LD_{50} = 217$ mgm./kgm.

Scatter of Observations—Mean and Standard Deviation: It has been seen that in all biological experiments, the observations are scattered around the mean, the mean being worked out from a statistically significant number of experiments.

For example in one set of experiments the observations may be 13.9, 15.1, 12.2, 16.1, 19.3; Mean = 15.3; $SD \pm 1.8$. In another set, 14.5, 18.1, 9.8, 21.5, 12.4; Mean = 15.2; $SD \pm 4.6$.

In both these sets of experiments, the mean is quite close but the scatter of the individual observations is different.

In the first, SD is ± 1.8 , whereas in the second, it is ± 4.6 , which obviously indicates that there is less scatter in the first and hence greater accuracy. This is the importance of SD determination in any experimental work.

Standard deviation is calculated from the following formula:

$$SD = \sqrt{\frac{sd^2}{n-1}} \quad \text{in which } Sd^2 \text{ is the sum of difference squared}$$

and n is the number of observations.

Standard error of the mean: Though SD provides an idea about the scatter of observations, a full and really accurate idea about accuracy and dependability of the mean, can be obtained only after determination of *Standard Error* of the mean. This is worked out by the following formula:

$$SE = \frac{SD}{\sqrt{n}} \quad \text{or} \quad \sqrt{\frac{Sd^2}{n(n-1)}} \quad SE = \text{Standard error of mean.}$$

Sd^2 = Sum of differences from mean squared
 n = No. of observations.

Lesser the figure of SE obtained, more accurate is the mean. SEs in the above 2 sets of observations are ± 0.3 and ± 0.5 , which means that the former mean is more accurate.

Significance of a Difference: This has an importance when the observations of two similar substances are to be compared from the standpoint of means obtained with a view to know whether one differs from the other in any significant manner. This is done by what is known as *T test*, as per the equation below:

$$T = \frac{m_1 - m_2}{\sqrt{e_1^2 + e_2^2}}$$

m_1 = Mean of the 1st set.
 m_2 = Mean of the 2nd set.
 e_1 = Standard error of the 1st.
 e_2 = Standard error of the 2nd.

Only when T is at least 2, it is significant. In the above example, mean 15.3, $SD \pm 1.8$ and $SE \pm 0.3$ in one set and in the other equivalent figures are 15.2 ± 4.6 and $SE \pm 0.5$.

T value for the above being 0.23, the difference is insignificant, i.e. the second sample is not appreciably weaker than the first.

Relative Potency and Fiducial Limits. These are worked out with the formula, $R = \frac{bT}{bS}$ where R = relative value, bT = test dose, bS = standard.

This is another way of finding out the significance of a difference between the standard and test, provided the *SD* figures in both are such that one is less than 50% of the other.

Binomial Distribution—Chance of Death and Probability of Error:

This, in fact, is a higher type of calculus, referring to probabilities or *P value*. It aims at establishing whether the observed differences in any two sets of measurements can arise by chance. The value is worked out by consulting a 'Probability Chart', giving 't' value. The significance ratio is obtained from the 't' table. A probability of one in twenty ($P < 0.05$) is statistically *significant* and less than 0.01, *highly significant*.

In bioassay, a sample has to be tested against a standard which has been worked out under different conditions of experimentation, the sample having much less number of observations than the standard and yet a quantal comparison is to be aimed at. To illustrate by example :

- (a) If LD_{50} dose is given to one mouse, mortality can be either 0 or 1, the two results being equally likely and thus giving a probability of 0.5, i.e. 50/50.
- (b) The same dose injected into 2 mice would produce a probability of (AA, DA, AD, DD—alive or dead). Expressed mathematically this will be $(\frac{1}{2} + \frac{1}{2})^2 = \frac{1}{4} + \frac{1}{2} + \frac{1}{4}$ i.e., in 25 % cases, no death, in 50 % cases, 1 death and; in 25 % cases two deaths.
- (c) Injected into 3 mice the probability will be $(\frac{1}{2} + \frac{1}{2})^3$. Expressed in the form of an equation, in a sample of 'n' the probability of $1/2^n$. The number of sequences of results in which there are deaths, by the theory of permutations and combinations, will come to

$\frac{n!}{x!(n-x)!} \times (1/2)^n$; ($x!$ = factorial x). If the dose tested is sufficient

to kill a proportion P , then the above expression becomes $\frac{n!}{(n-1)!} \times PQ^{n-1}$, i.e. $Q = (1-P)$.

By working the probabilities with various formulae, Durham, Gaddum and others have established P of E for different number of animals as detailed below (Table 4).

TABLE 4

Toxicity of samples	Percentage of tests in which sample will pass		
	30 mice	20 mice	10 mice
100	100	100	99.8
110	99.9	99.6	98.0
120	76.9	75.1	73.8
130	6.5	12.2	24.8
140	—	0.2	3.3

From the foregoing, it is evident that bioassay, which as *quantitative pharmacology* is concerned with the quantitative measurement of drug action in terms of accepted standards, is extremely complex and involves not only special and delicate techniques but also following of special principles of assessment and biometry for attaining quantal and significant results. The important points for consideration are:

- (a) Preparation of solutions of standard and test and methods of experimentation under identical conditions, using simple techniques and calculations and avoiding assumptions. Even when the ST and T are known to be qualitatively the same this is to be tested for *validity*.
- (b) Determination of the sensitivity of the preparation and the power of discrimination by slightly varying the dose and also working at submaximal dose level for utilising the discriminating power of the preparation to the maximum.
- (c) Maintaining standard dose response fixed and varying the test response to lower, higher and ultimately to equiresponse level of the standard, side by side, ensuring that the sensitivity of the organ has not changed during the process of experimentation.
- (d) The newer design of 4 point assay of Bulbring, Burn and Schild, using 2 doses of the standard and 2 doses of the test should be made use of whenever possible.
- (e) The accuracy of the assay should be determined by plotting the dose-response curve with log doses of ST and T. From the linear and parallel relationship of both, the relative strength should then be calculated.

ASSAYS

Digitalis: International standard powder prepared by pooling of different samples of digitalis leaves and stored in nitrogen filled ampoules in NIMR, London. Unitage, 80 mg 1 Unit. There are four methods of assay, based mostly on toxicity.

(a) *Cat method* (B.P.) of Hatcher and Brodie. Cats weighing 1.7-2.7 kg. are anaesthetised with oral chloralose and diluted tincture—1 in 20 is perfused through the femoral vein at a uniform rate in 6 cats. The end—point is recorded from the carotid pressure. The LD figure of sample is compared with that of the standard (17.17 ± 20 per cent, obtained in C. D. Lab. from 30 cats.).

(b) *Guineapig method*, used mostly in France, is similar to the above

but perfusion of 1:8 tincture through the jugular vein and end point determined by pinning the apex of the heart.

(c) *Frog method* (USP): LD worked in a large number of frogs and the average compared with the standard figure.

(d) *Pigeon method*: Infusion of tincture through the alar vein and emesis taken as the end point. Result compared with the standard figure.

Post Pituitary Extract: (a) International Standard, 0.5 mgm. = 1 I.U. The extract is made with 0.25% glacial acetic acid and ST and T made to have the same dilution. (b) The assay is carried out by comparing the oxytocic activity of sample with the ST in virgin guineapig uterine horn, animal weighing between 150-200 gm. $\pm 20\%$ margin is allowed.

Insulin: The standard crystalline powder is prepared and supplied by the Insulin Committee of Toronto and kept in vacuo over P_2O_5 , each mg. representing 22 Units of activity. The assay is carried out either by rabbit blood sugar or mouse convulsion method.

Blood sugar method: (a) In this, rabbits of 1.5–2 kilos, kept on prescribed diet, have 1 unit of insulin S.C. in the morning for finding out the sensitivity. (b) If no convulsion occurs they are divided into two equal groups, one group having the standard and the other the test. (c) Blood is collected from ear veins before and every hour after insulin for 5 hours and blood sugar estimated by Hagedorn—Jensen method on pooled serum, by the titration method. (d) Cross-over tests may also be carried out and the relative potency of St. and the sample determined. $\pm 10\%$ is the permissible limit.

Mouse convulsion method: In this case, also, the underlying principle is to determine the dose of the unknown which produces hypoglycaemic convulsion in the same % of animals as with the standard.

Adrenaline: (a) A natural powder of -50° – -52° optic rotation is used as the standard and made to 1 in 20,000 or 1 in 40,000 dilution. (b) The assay is carried out by 'Elliot's Spinal Cat method', with initial ether and artificial respiration. (c) When the carotid pressure is steady after elimination of ether, the Standard and the Test are compared from their pressor response on the cat. $\pm 10\%$ is the permissible margin.

Oestradiol Monobenzoate is the international standard; 0.001 mgm. representing 1 I.U. of activity.

The assay is carried out by *vaginal smear method* in ovariectomised mice. (a) During oestrus, the smear shows thick epithelia with nucleated and cornified cells, and during dioestrus, the surface becomes thin with leucocytic infiltration. After bilateral ovariectomy the picture is as during dioestrus. (b) After verifying the result of successful operation, the mice are divided into 2 groups. Oily solution of St. & T are then given SC to different batches of operated mice and from the 3rd or 4th day, scores on the degree of positive responses given to both the batches for comparison. The allowable margin is $\pm 20\%$.

Progesterone: (a) International Standard, 1 mg. = I.U. (b) Immature rabbits of 750 G. are treated with oestrone, 25 units/day for 6 days, followed by progesterone, 0.5 mg./day from the 7th to the 11th day. (c) Section of uterus is then prepared, degree of proliferation of uterine glands compared in ST and T series—1st to 4th degree (simple proliferation being the 1st and invasion of endometrium the 4th degree). In this way, potency of sample is determined.

Androsterone: (a) Capon's comb test. Leghorn is anaesthetised, testes removed and ST and T injected I.M. for 5 days in 2 separate groups. From the degree of the growth of the comb in the two groups, relative potency is determined. (b) Rat prostate and seminal vesicles method. Castrated rats are treated with ST and T separately and weight of the prostate and the seminal vesicles compared in the two groups for calculation of the relative potency of the sample.

Anterior Pituitary Hormones: (i) *Thyrotropic hormone* is estimated from increase in weight of *thyroid* gland in female guinea pigs, (ii) *Prolactin* is estimated by crop gland method in pigeons. (iii) *Growth hormone:* (a) Hypophysectomised rats of 100 gm. are divided into three groups of 10 each. Standard is given to two groups with doses in double of the other and test in one group with an intermediate dose. (b) After hypophysectomy, rats are kept on fixed diet for one week for keeping constant weight during assay. From the rate of growth in the 2 series, the potency of the preparation is determined and compared with the Standard. (iv) *Gonadotropic hormone.* There are a large number of assay methods for this hormone; e.g. (a) vaginal smear and uterus weight methods and also increase in weight of male organ and ovaries in rats, and (b) estimation of luteinisation of ovaries in female rats by histological examination, after injection of ST and T in different groups and searching for corpora lutea.

Thyroid Hormone: is assayed by 2 methods principally: (a) rate of metamorphosis in tadpoles, and (b) rate of O_2 consumption and CO_2 excretion in mice. The latter which is more accurate is preferred. The underlying principle of assay, is the same as in other cases, the sample being compared against the standard side by side and the percentage of potency of the unknown is thus worked out.

Vitamin D: Crystalline vitamin D, calciferol or irradiated Ergosterol in olive oil solution is used as the international standard for the assay of samples. The methods in use are (i) the line test with $AgNO_3$, (ii) X'ray examination of bones, and (iii) estimation of % of ash.

Young rats of 50-60 gm. body weight, obtained from parents kept on reduced vitamin D diet, are used for the assay. Ricket is induced in them by rachitogenic diet and altered ca/phos. ratio in diet and being kept in rooms, cut off from sunshine. When the rats do not grow some of them are sacrificed and distal ends of radius and ulna examined with 1.5% $AgNO_3$ solution. The black area denotes the epiphyseal area and its width is the measure of the degree of rickets induced. This is known as *line test*. The ricketty rats are then grouped into different batches and from the comparative curative effect of standard and test solutions, relative potency is worked out.

Organic Arsenicals: The assay comprises of the determination of (a) toxicity, and (b) therapeutic efficiency in suitable laboratory animals.

Toxicity Test is carried out on mice or rats, of 18-20 g. and 100 g. weight respectively.

The LD_{50} dose for neoarsphene already worked out as 0.58 mg./gm. body wt. in mice. 5/6th of this dose of the T is injected into the tail vein of a set of 10 mice initially. If 2 out of 10 mice die in 72 hrs. the sample passes.

If more than 2 die, the dose is injected into another 10 mice and if less than 8 die, the sample passes.

If more than 8 die, another 10 mice are injected and if the total mortality in three batches exceeds 15, the sample is rejected.

Therapeutic Efficiency Test is carried out in infected rats and guinea-pigs with Trypanosoma Equiperdum by the usual protective and survival effects of ST as compared to samples from examination of peripheral trypanosoma by giving different scores from the degree of removal of parasites.

Adrenaline and Noradrenaline in a Mixture: The method is based on the fact that rat uterus is more sensitive to adrenaline while rat colon

to noradrenaline. Amount of adrenaline is estimated on rat uterus by studying its inhibitory effect vis-a-vis acetylcholine. Similarly, noradrenaline is estimated on rat colon vis-a-vis acetylcholine or carbachol.

Acetylcholine, 5Ht and Histamine: Basic principle is to find out the dose of the unknown required to produce the same degree of response as that of standard, on isolated preparations.

For acetylcholine *Frog rectus* is suspended in leech apparatus and sensitised to Ach by eserine. Contractions are recorded by Gimbal lever. Prior atropinisation of the preparation is necessary to block the effect of cholinergic substances.

Quinidine Substitutes: *Isolated rabbit auricles*, suspended in Ringer-Locke solution, are stimulated by square wave stimuli at the rate of 250-300/mt. till beats start dropping. Relative potency of the drug is then determined from the degree of reduction in the auricular rate.

Curariform Compounds: (a) *Rabbit head drop.* Test drug is infused through the marginal ear vein and the dose producing HD_{50} is compared with that of standard. (b) *Isolated rat diaphragm and cat gastrocnemius:* Control contractions produced by stimulation of phrenic or sciatic nerve are recorded. The potency of ST and T is compared from their inhibitory effect on these contractions.

CHAPTER

7

CONCEPT AND SCOPE OF GENETIC PHARMACOLOGY

GENERAL CONSIDERATIONS OF CHROMOSOMES AND GENES AND THEIR ANOMALIES. DRUG INDUCED GENE DISORDERS AND DRUG RESPONSES IN GENETIC DISORDERS. SCOPE AND LIMITATIONS OF PHARMACOGENETICS.

[Man's curiosity for understanding the hereditary nature of disposition of hair, polydactyly, albinism, and mongolism goes to the remote past. It was, however, the work of Darwin, Galton and Mendel on evolution, eugenics and heredity that paved the path for systematic genetic studies. Since then, with the advances in the knowledge of the biochemical aspects of cell-components, chromosomes, nucleic acid, D.N.A., R.N.A. and genes, that our knowledge of pharmacogenetics has emerged as a distinct subject of study.

The chromosome number is now fixed at 23 pairs per cell with thousands of genes in each, which are responsible for protein synthesis through genetic codes, many metabolic functions and also transmission of hereditary traits through mitosis and meiosis of cells. It is now known that amino acid synthesis by ribosome is highly intriguing and involves operations of various types of genetic actions through histone, disturbances resulting even in lethal mutation.

Genetics is incriminated in (a) Developmental, (b) Blood group, (c) Inheritance, (d) Congenital, and (e) Abnormal drug response anomalies. Chromosomal anomalies may implicate structural deviations as in translocation, deletion or additional number, observed in Kline-Felter and Turner syndromes, hermaphroditism, etc. In trisomy, there is an extra autosome as observed in mongolism, Patau and Edward's syndromes. Genetic factors are also operative in a number of diseases like otosclerosis, congenital dislocation of hip, club-foot, diabetes, hypertension, peptic ulcer and even certain varieties of cancer, with varying degrees of '*geno*' and '*pheno*' types of blendings.

It is established that '*Drug responses*' also vary in gene disorders, e.g. succinylcholine and atypical cholinesterase, primaquine sensitivity in G-6-PD, isoniazid rapid and slow excretion, inability of phenylthiourea tasting, inherited resistance to coumarine anticoagulant action. Similarly, '*Drug induced gene disorders*' entail teratogenic effects as in thalidomide phocomelia, corticosteroid cleft-palate, etc. Physically induced gene disorders from ionising radiations may produce point mutation, besides the usual somatic cell destructions.

Results obtained by study of drug action in restricted species of animals may not offer '*predictability*' of exactly similar responses in man. Individual variation is almost a '*Law of Nature*', and even identical twins do not behave in similar manners. The *genotype* combining with *phenotype* and the former being further influenced by *mono* and *multifactorial* inheritances, create enormous differences. Man is a very distinct species and must be different from others in genetic set up. Therefore, predictive pharmacology may not work from animal tests only.

All these refer to the '*scope and limitations*' of pharmacogenetics, and explain how a large number of diseases, as well as, aberrant drug responses, drug resistance, tolerance, idiosyncrasy, biological variations, abnormal cellular metabolism in respect of certain drugs, might revolve around certain genetic links. Lastly, the importance of human genetics in the study of anthropology and racial responses to certain drugs and diseases, cannot be ignored. Pharmacogenetics is a promisingly expanding field and may one day engulf many psychic and somatic disorders, drug addiction and many other aspects of study, proceeding from the known to the unknown, with accumulated knowledge of intricate mechanisms of cellular functions, as well as complex actions and interactions of drugs at molecular and submolecular levels.]

Pharmacogenetics is one of the latest additions to the expanding field of scientific Pharmacological studies, which have brought out revealing facts in respect of genetics, as well as, drug responses in man and animal, in gene disorders.

Though observational knowledge on heredity and eugenics had been existing almost from pre-historic days, in respect of disposition of hair, polydactyly, albinism, hermaphroditism and mongolism, it is the systematic work of Mendel and others that has scientifically established the nature of transmission of heredity in plants and animals on a sound footing. With advances in our knowledge of cell-components, nucleus, chromosomes, D.N.A., R.N.A., special mechanisms of protein synthesis in ribosome through genetic codes, that we understand better the role of genetics in normal and abnormal functioning of individuals vis-a-vis drugs and diseases.

There are enormous number of chromosomes and genes per cell of the body which are not only concerned with the transmission of hereditary traits, but also protein and aminoacid synthesis, control of metabolic and other vital cellular functions of the body. Its scope has further been enlarged with the linking of blood group genetics, biochemical genetics and also eugenics along with it.

Some Fundamental Aspects. Each cell nucleus contains 23 pairs of chromosome bearing thousands of genes. The chromosomes are divided into (A) Sex—Chromosomes—xx in females and xy in males, and (B) Autosomes. With the discovery of the role of nucleic acids as essential components of hereditary material and more elaborate knowledge of D.N.A., m-R.N.A. and their working through genetic code in aminoacid synthesis by the ribosome, we know better the intricate mechanisms of repressor, derepressor, regulator, operator and control genes and how abnormal protein synthesis through dege-

nerate, nonsense and missense codes, may occur. It is now established that the gene activity is controlled at the molecular level through histone which plays an important role in the operation of a network of genetic switches comprising of nucleoproteins and hormones, the disturbance of which, may be responsible for genetic mutation and formation of lethal mutants. With all this knowledge, it is now possible to understand better the working of genetic controls in hereditary and other diseases, as well as, in unpredictable drug responses and biological variation in man and animal.

It is established that the development of a foetus, its repeated mitotic division, segregation of specialised cells to form tissues and organs in a coordinated manner, are under some unified control with repression and derepression of gene loci. Similarly, geographic distribution of different blood groups in different races in parts of the world, with preponderance of certain diseases, are in support of their genetic origin. For obvious reasons, different types of inheritances of dominant and recessive traits on chromosomal or autosomal paths occur through parental genes. Osteogenesis imperfecta, achondroplasia, fibrocystic pancreas, alkaptonurea, galactosaemia and albinism are explained in this manner.

Chromosomal anomalies may involve structural changes as in (a) Translocation (b) Deletion, and (c) Missing or additional chromosomes, which may be responsible for Klinefelters syndrome with xxy or xyyy, instead of xy chromosome, with small testes and prominent breast in males, Turner's syndrome from xo sex chromosome with sterility and amenorrhea in female and true hermaphroditism with chromosomal mosaicism, some cells having xx while others xy sexchromosomes may occur. *Autosomal* aberrations may induce (a) Anueploidy with loss or gain of one or two chromosomes, (b) Polyploidy involving a whole set of chromosomes, and (c) Trisomy with an extra autosome as in (i) Mongolism, (ii) Patau's syndrome, with an extra xx D group, and (iii) Edward's syndrome with an extra C group.

Clinicopharmacological Aspects. These may be considered under the following heads : (a) Genetic factors in diseases, (b) Drug response in gene disorders, (c) Drug induced gene disturbances, (d) Predictable and unpredictable drug responses, and (e) Biological variations.

Genetic Factors in Diseases. Besides those already mentioned, only a few rare diseases are of exclusive genetic origin and others are often a combination of *geno* and *phenotype*, i.e. having different degrees of both genetic and environmental influences as revealed by pedigree

studies of identical and non-identical twins, who if similarly affected are considered to be *concordant*, while otherwise *disconcordant*. From the study of heritability, the degree of genetic and environmental impacts are determined, which give a percentage figure of 80 for congenital dislocation of hip, 70 for club-foot, 65 for coronary artery disease and 40 for gastro-duodenal ulcer.

Diabetes mellitus is inherited as an autosomal recessive trait; *hypertension* arises out of a dominant gene and is concordant in identical twins. *Peptic ulcer* is a phenotype inheritance associated with blood group 'O' in some races.

Drug Response in Gene Disorders. The term *Pharmacogenetics* introduced by *Vögel*, means genetically determined variation in drug responses detectable only after administration of those agents. Works of Williams (1956) and others, have proved that each individual is a separate pharmacological and biochemical entity, as determined by the functioning of proteins, enzymes, hormones and other essential constituents in the body, which may even sometimes be correlated to family incidences. This may also explain the phenomenon of idiosyncrasy in certain individuals and racial and species variations in man and animal. Some of these conditions are as under:

Succinylcholine and Atypical Cholinesterase. This is an interesting observation of genetic nature observed in recent years. Succinylcholine—a short acting muscle relaxant is destroyed by an atypical pseudocholinesterase. If this is low in the plasma of certain individuals, they show dangerously prolonged effects. Leyman (1956) ascribed it to a homozygous autosomal recessive gene. *Dibucaine*, the local anaesthetic, inhibits this esterase, which is expressed in terms of (DN)— E_1 and E_2 representing normal and atypical enzymes. The genotypes thus may be E_1E_1 ; E_1E_2 and E_2E_2 with corresponding phenotypes, of DN 80, 60 and 20 respectively. There are thus six possible types of combinations each producing offspring of particular genotype.

Primaquine Sensitivity. The massive haemolytic episode with primaquin, has now been shown to be due to a deficiency in the red cells of the enzyme Glucose-6-phosphate dehydrogenase (G6PD), of genetic origin. These primaquin sensitive individuals are also sensitive to pentaquin, phenacetin, acetanilid, aspirin, phenyl-hydrazine, furadantin, certain sulphonamides, benemide, tolbutamide and β -naphthol. The mechanism is still unknown.

Acetophenetidine O-Dealkylation. This unusual response was observed in a Swiss family by Shahidi (1968). Acetophenetidine is metabolised in man by O-deethylation to 2-N-acetylpara-animophenol. The latter is then conjugated as glucuronide and sulphate derivatives, in the liver. Persons deficient in liver microsomal dealkylase, metabolise acetophenetidine to O-aminoparaphenol, a toxic metabolite, causing methaemoglobinaemia and haemolysis.

Glucuronide Conjugation. This is a very common detoxicating mechanism of drugs, bilirubin and several other endogenous substances. In *Criggler-Najjar Syndrome*, there is reduction in the conjugation of bilirubin, accompanied by severe non-haemolytic jaundice and cerebral disturbances. The patients show reduced ability to form glucuronide conjugates of menthol, salicylates and tetrahydrocortisone, as the same transferase enzyme system catalyses the conjugation of bilirubin and also of these drugs.

Isoniazid. This drug is inactivated by the process of acetylation. Of the two classes of persons, the (a) *Rapid* and (b) *Slow inactivators*, the latter are homozygous for an autosomal recessive gene, with a half life of 170 minutes in the plasma, while the *Rapid inactivators* are homozygous for a dominant gene, with a half life of 60 minutes. There is a bimodal distribution and a genetic control to the extent of 97%, as revealed in identical paternal twins. The children of slow inactivators are normally slow excretors, but those of the other group, are of both types. The Eskimos and the Japanese have only a small proportion of slow excretors.

Taste of Phenylthiourea. The ability to taste phenylthiourea is inherited. This finding has proved to be a useful tool not only in genetics, but also in anthropological studies. Pathologic states of the thyroid gland have been correlated with the ability or otherwise, of tasting phenylthiourea.

Inherited Resistance to Coumarin Anticoagulants. Reilly *et al* (1964), found an inherited resistance to the anticoagulant effect of coumarin derivatives, to the extent to 20 E.D. unrelated to any faster rate of metabolism or protein binding. They were unusually sensitive to Vit. K, again to the extent of 20 times. The resistance is inherited as an autosomal dominant trait.

Heritable Factors in Animals. A word in passing about some of the heritable factors in animals, about which, we know so little as yet,

excepting that Sawin and Glick (1943) demonstrated the presence of atropinesterase in the rabbit serum of certain strains, genetically controlled by a single dominant gene and that certain strains of mice can stand LD 300 of insulin, and that slow inactivation of antipyrine may occur in certain strains of rats. The problem needs much greater elucidation than what has been done so far.

DRUG INDUCED GENE DISORDERS

As genetic disorders modify drug actions, likewise, toxic chemical substances, acting at enzymatic level, might induce structural and functional changes in genes. The action of a number of chemotherapeutic, antibiotic and antimalignancy agents, thalidomide and corticosteroids, attests to this. Similarly, physical agents can also induce genetic mutations.

Teratogens can induce foetal anomalies in chick embryos. The incubated eggs are examined by transillumination upto the 10th day or beyond and the dead chicks are then examined for internal and external abnormalities.

The teratogenic effects of nivaquine, trypan blue, insulin, cortisone and INH have been expressed in a number of anomalies-clubfoot, dislocation of hip, micromelia, exomphalocoele, parrot beak, etc. In other cases, which are numerous and uncertain, viz. thalidomide phocomelia, corticosteroid cleftpalate, various types of myopathies and virilisms, cobalt thyroid dysfunction, atropine induced acute angle glaucoma, hydralazine lupus, chloroquine scotoma, trimethadione nephrosis and chlorpromazine parkinsonism which are usually taken as toxic manifestations, may also deserve careful explorations for elimination of any genetic linkage. Similarly, the psychogenic drugs, LSD-25 and Cannabis indica may also merit some genetic studies, through successive generations.

Another aspect of the problem is *Ionizing radiation* which causes serious damages to the living tissues by electronic disturbances from the electromagnetic waves of β and γ rays. Besides the somatic troubles, bone marrow depression and tissue destruction, the genetic disturbances are mutation, chromosomal deletion, segmentation, and even *point mutation*. The effects of radiation are cumulative, from generation to generation, and the mutation may also be caused by radioactive fallouts. In the same manner, *cytotoxic agents*, formaldehyde, toxic dyes, certain metabolites and even caffeine have been suspected of some genetic effects, for which further studies are essential for clinching the correct position.

Unpredictable Drug Responses and Biological Variations. Two other closely associated pharmacological problems are the Unpredictable Drug Responses and Biological Variations.

The predictive value of drugs no doubt depends on their nature, designing of experiments and accuracy of techniques, but on the basis of the recent observations, it is evident that for an accurate assessment of drug action, animal and human studies in selected fields, have to be combined, in some form or other.

From an analysis of drugs already introduced, it appears that this is true for drugs acting virtually on all the systems. The complex action of chlorthiazide in hypertension, the extent of predictability of adrenergic beta blockers, toxic potentials of antifertility drugs, corticosteroid cholestasis, 6-azauracil behaviour in the body, and also intricate mechanisms of psychopharmacologic and C.N.S. drugs, all attest to this. It took decades to detect the adverse effects of phenacetin, thalidomide, reserpine and even penicillin, till sufficiently large number of human trials were possible. It is a common knowledge that not only toxic effects but also pharmacotherapeutic actions of drugs vary from species to species and from individual to individual. There must be valid reasons for this beyond the prevailing concepts of age, sex and environmental factors, and who knows, whether some of them are not of genetic origin. There could not be only one yardstick of measurement of physio-psychological components of individuals, as a large number of diversely operating factors create enormous differences. Individual variations may be narrowed but not fully eliminated. While animal experimentation is essential, human studies in respect of drugs, are equally important. Unpredictable hazards would occur if drugs are not studied on a large cross-section of human population of different social and genetic patterns. We have, thus, to dovetail our drug studies in animals and human beings and also enforce genetic screening of drugs as a routine measure, which only will offer better chances of predictability in drug action.

Scope and Limitations. From the foregoing, it is apparent that both genetics and pharmacogenetics, within such a short span of time, have already made profound impacts on most of the fields of medicine and science.

Study of drug resistance in bacteria and insects implies uses of genetic methods which have great clinical significance and applied value. Similarly, knowledge of protein and enzyme synthesis in the body, metabolism in general and drug metabolism in particular, cellular metabolism and biochemical reactions, the concepts of heredity and

eugenics, are all of utmost value to human beings. As more knowledge is gained, it may be possible, sometimes in future, to predict in a mathematical way, the incidence of abnormal responses based on frequencies of known genes, in a population. Further, knowledge of pharmacogenetics might explain tolerance, resistance and drug hypersensitivity reactions in individuals. The more one would learn about the genetic linkage in man, the more effective will be his genetic counselling. With increased knowledge, one may be able to tell a person from his blood group, or from the shape of his finger nails, or from his ability to taste phenylthiourea, whether or not, he is predisposed to a disease which has occurred in his family.

Lastly, one cannot minimise the usefulness of the knowledge of human genetics in anthropology. The observations of simple gene characters offer by far the best means of measuring the degree and rate of racial intermixture and this may permit one to understand better, the tracks of origin of populations.

However revealing all these may appear to be, one cannot forget that no finite knowledge is easily attainable. With the limited advances already made, the world of genes does not appear to be less complexly functioning than our gross body. This complexity is the scope and limitation in scientific advancement. As more riddles are solved, fresher ones will appear, the progress will continue, but the last word will still remain to be said, probably for ever.

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SECTION
III
PHARMACOLOGY OF AUTONOMIC DRUGS
CHAPTER
8
GENERAL CONSIDERATIONS OF AUTONOMIC
NERVOUS SYSTEM

SOMATIC AND AUTONOMIC SYSTEMS — THEIR DIFFERENCES AND
DIVISIONS; PHYSIO-ANATOMIC CONSIDERATIONS. CHEMICAL
MEDIATION, RECEPTORS, ANALYSIS OF ACTION

[Of the two sections of the nervous system—the somatic and the autonomic, the former, as cranial nerve, supplies the locomotor system and skeletal muscles. The latter, also known as visceral efferent, innervates the internal organs, not under any volitional control. The parasympathetic which is of cranio-sacral origin, and the sympathetic of spinal or dorso-lumber origin, have essential differences, not only in respect of origin but also about distribution of ganglia and essential functions on different organs—eyes, C-V and respiratory systems, G.I. Tract, urinary bladder, etc. often working mutually antagonistically, the level of regulatory functions depending upon the finer balancing of the two components of action.

The impulses in both these systems associated with electrical changes, as well as, liberation of certain specific chemical substances at different steps—preganglionic fibres, ganglion, and endings, postganglionic fibres, endings and receptors. This is acetyl choline, all through, for the parasympathetic system but noradrenaline at the last stage only for the sympathetic. These transmitters combine with receptors in the effector organ, to produce the desired effect and are then destroyed by suitable enzymes cholinesterase (CHE) or amine oxidase. Autonomic ganglia and neuromuscular junction behave similarly and their stimulation, mediated by Ach, produces nicotinic type of action. Similarly, stimulation of postganglion cholinergic fibres produces muscarinic type of action. The cholinergic receptors, depending on their location-ganglion, n.m. junction or postganglionic nerve endings—are hexamethonium, curare or atropine sensitive. The sympathetic or adrenergic receptors are of three types : (a) *alpha-receptors* — responsible for vasoconstriction and intestinal relaxation — are blocked by ergot, (b) *Beta-receptors* — responsible for broncho-dilatation, intestinal relaxation and cardioacceleration, are blocked by DCI (dichloro isoprenaline) and (c) metabolic or *mixed receptors* — concerned with glycogenolysis and hyperlipaemia, are blocked by Isopropyl methoxamine. Thus selective paralysis of these various components of the parasympathetic, sympathetic system as well as, of neuro muscular junction can be produced by available drugs for study of their mode of action and therapeutic possibilities.]

In order to understand clearly the effects of drugs on various systems of the body, it is necessary to study the pharmacological responses of the nervous system first, which comprises of *two important sections*:

Somatic Nerves: supplying skeletal muscles.

Autonomic Nerves: supplying involuntary muscles and organs.

Each one of them consists of a *central* and a *peripheral* component. The main points of differences between these two systems are:

<i>Organ and action</i>	<i>C. N. S.</i>	<i>A. N. S.</i>
Fibres	Medullated ;	Nonmedullated ;
Synapses	Within C. N. S.	In ganglia outside the Cerebrospinal axis
Section	Paralysis of muscle	Autonomic activity continues
Excitability and Conductibility	Marked ; quick	Slow and tonic

The term, A.N.S., introduced by Langley, is also known as *visceral efferent* or involuntary nervous system, which unlike C.N.S., is not under volitional control. It consists of nerves, ganglia and plexuses, which innervate the heart, blood vessels, glands, smooth muscles, and certain internal organs. It is widely distributed all over the body and controls those functions, which go on unconsciously, like the beating of the heart.

Anatomically—the system is divided in two parts: (a) Parasympathetic and (b) Sympathetic.

The common features of the two divisions are: (a) Cells of origin—in the C.N.S. (b) Definite mechanism of central integration. (c) Ganglia — outside the C.N.S. (d) Two neurons—preganglionic and postganglionic, and (e) One synapse — in the ganglia.

Preganglionic Neurone or Fibre is *medullated*, leading to the ganglion, and is *cholinergic* in nature.

Ganglion: a collection of nerve cells, serving as a centre of nervous influence. It is also *cholinergic* in nature.

Post-Ganglionic Fibres: non-medullated, extending from the ganglion to the effector organ. The number of fibres leaving the ganglion, their length and the chemical substances liberated at their endings, depend on the respective division of the A.N.S.—viz. *Parasympathetic or Sympathetic*.

Plate VIII

ANATOMICAL DISTRIBUTION OF THE AUTONOMIC NERVES

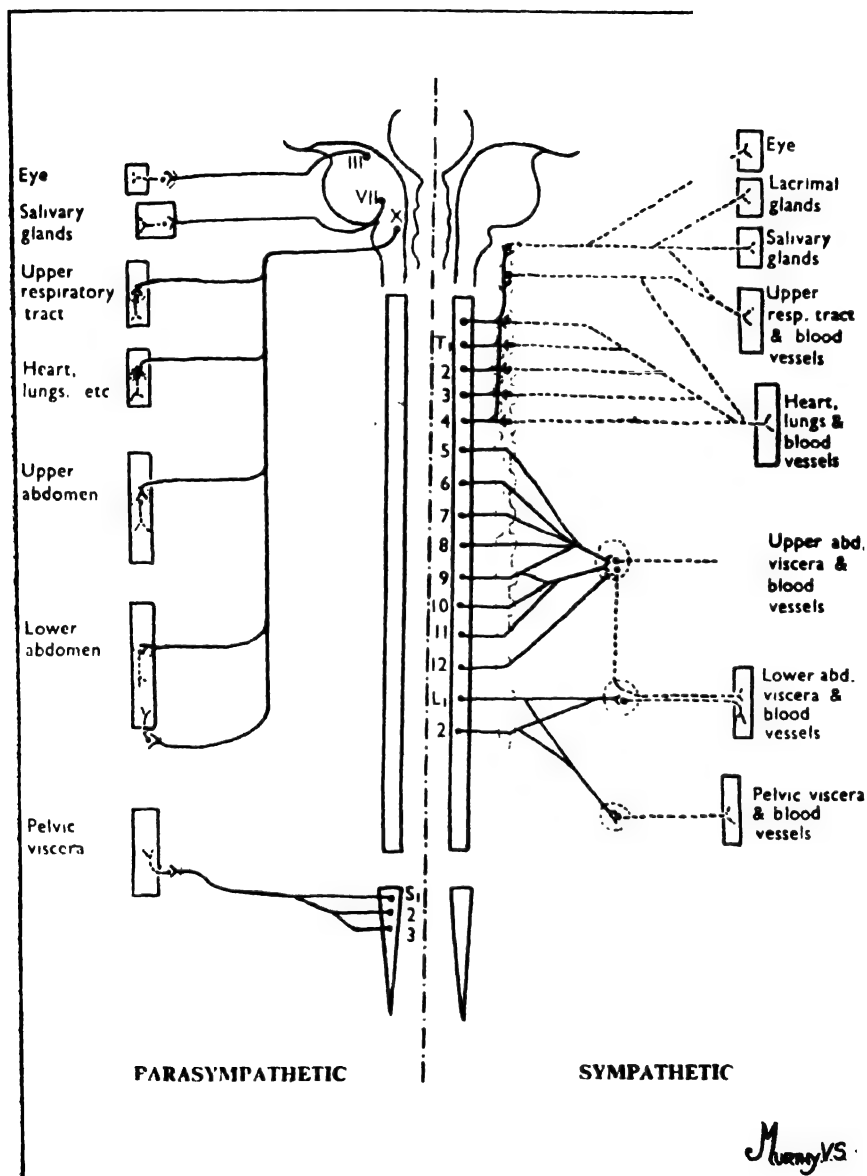


FIG. 25. Parasympathetic and sympathetic sections

PHARMACOLOGY OF AUTONOMIC DRUGS

Anatomical Considerations: Particulars in respect of origin and distribution of the two systems (Plate VIII; Fig. 25) are as follows:

PARASYMPATHETIC SYSTEM

	Origin	Preganglionic fibres	Ganglion	Postganglionic fibres
TECTAL OUT-FLOW	Anterior Quadrigeminal bodies	C. N. III	Ciliary	Iris, Ciliary muscle
BULBAR OUT-FLOW	Medulla	C. N. VII, C. N. IX C. N. X	In or near the organ of supply	Salivary and lachrymal glands, mucous membrane of nose, mouth and pharynx, Lungs, bronchii, heart, stomach and small intestine
SACRAL OUT-FLOW	II, III and IV Sacral segments	Sacral nerves	In organs of supply	Large intestine, rectum, urinary bladder, reproductory organs

Sympathetic System: *Thoracolumbar out-flow* : cells of origin lie in lateral horns of the spinal cord from T₁ to L₂ segments.

(1) *Preganglionic fibres* come out with the spinal nerves (white ramii) and travel to the ganglia which are arranged in three groups:

(a) *Vertebral*: along each side of the vertebral column. (b) *Pre-vertebral*: Coeliac, mesenteric and hypogastric. (c) *Terminal*: near bladder and rectum.

(2) *Post-ganglionic fibres* (grey ramii): are widely distributed and travel along the blood vessels to the organs of supply.

POINTS OF DIFFERENCES

	<i>Sympathetic</i>	<i>Parasympathetic</i>
Origin	Spinal	Cranial and Sacral 3, 7, 9, 10th nerves.
Distribution	All over	Limited to certain organs.
Function	Essential for stress and strain	Essential for maintenance of life.
Transmitter	More than one	One only

Physiological Considerations: Many organs receive nerve supply from both the divisions of A.N.S. In general, the effects of the two divisions

are antagonistic to each other, except in the case of salivary glands, where the effect is parallel. According to *Cannon* — the sympathetic acts like “The soft and loud pedals of a piano, modulating all the notes, whereas, the parasympathetic holds individual keys for these notes.” According to *Clark* — “The sympathetic acts like spurs and the parasympathetic reins of a horse.” The sympathetic is necessary for *fight* or *flight*, while the parasympathetic is essential for normal body functions. The opposing actions of the two divisions are important for preserving the organism in a state of optimal balance or homoeostasis.

RESPONSES TO NERVE STIMULATION

<i>Effector organs</i>	<i>Adrenergic response</i>	<i>Cholinergic response</i>	<i>Nature of response</i>
Eye			
Pupil	mydriasis	miosis	opposed
Ciliary muscle (accommodation)	—	Contraction for near vision	—
Nictitating membrane	contraction	—	—
Secretions —sweat & saliva	increased	increased	parallel
Bronchioles	relaxation	contraction	opposed
Heart	acceleration	slowing	opposed
Blood vessels			
coronary	contraction	relaxation	opposed
	relaxation	constriction	opposed
<i>other vessels</i>	constricted	dilated	opposed
G. I. Tract			
muscle wall	relaxation	contraction	opposed
sphincters	contraction	relaxation	opposed
Urinary bladder			
fundus, trigone & sphincter	relaxation	contraction	opposed
	contraction	relaxation	opposed

CHEMICAL MEDIATION AND IMPULSE TRANSMISSION

Impulses travel along the autonomic and motor fibres by means of electrical changes, as well as, liberation of certain chemical substances at synapses and nerve endings. The specific substance liberated at the nerve ending is known as *transmitter* and this combining with the receptor — a specifically designed area in the effector cell, evokes the characteristic response. The parts of an autonomic pathway (Plate IX; Fig. 26) are as follows:

Preganglionic fibre and ending → ganglion → postganglionic fibre and ending → autonomic receptor.

Plate IX

TRANSMISSION OF IMPULSES IN AUTONOMIC AND MOTOR NERVES

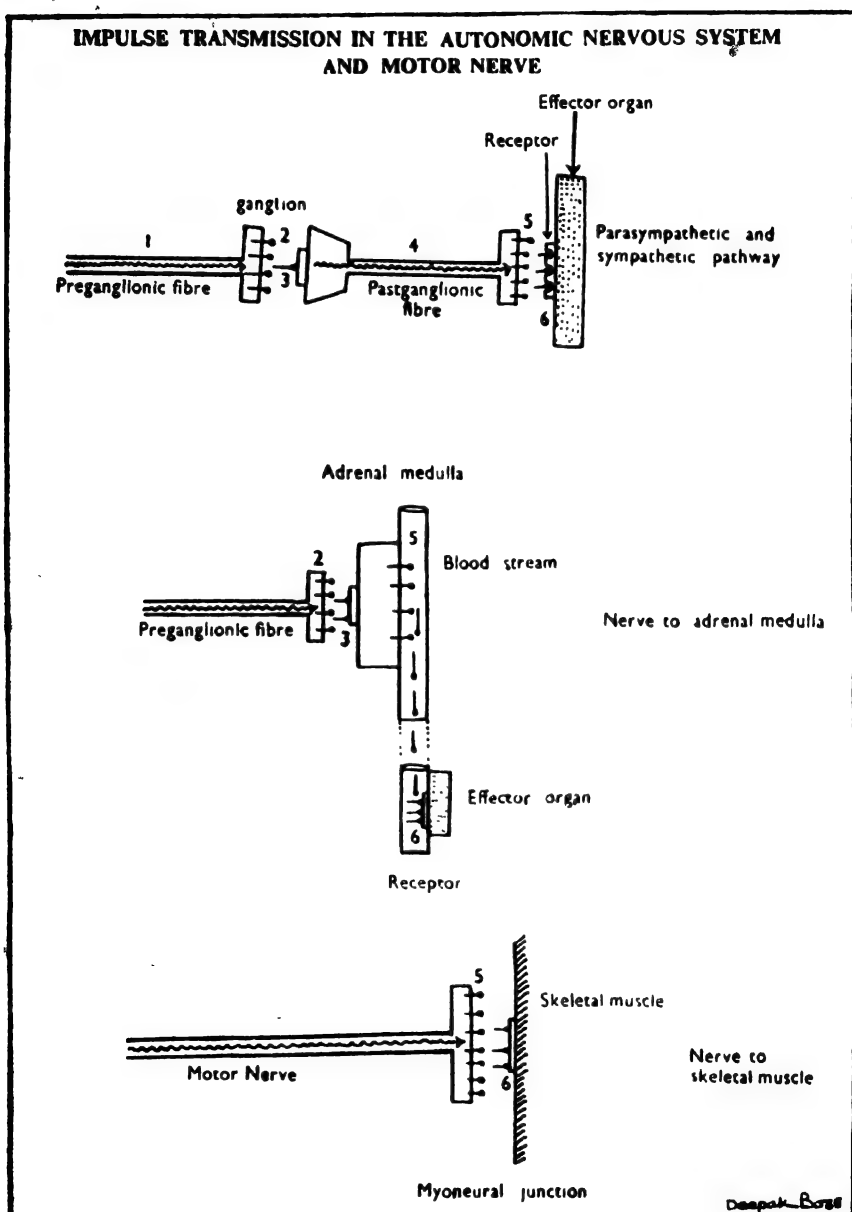


FIG. 26. Parasympathetic and sympathetic pathways, nerve to adrenal medulla and skeletal muscle

Stimulation of the receptors lead to certain actions in the effector cell of the tissue, supplied by the autonomic nerve.

The adrenal medulla is just like a sympathetic ganglion with this difference that instead of continuing further as a postganglionic fibre, it directly liberates adrenaline into the blood.

The motor fibres to skeletal muscle do not have any synapse like the autonomic fibres but an *end-plate* at the nerve ending or the myoneural junction.

In the above Plate, *Steps 1 and 4* represent the passage of electrical impulses along the pre and postganglionic fibre.

Step 2 is the liberation of acetylcholine by the preganglionic fibre in the ganglion.

Step 3 (a) is the combination of this acetylcholine with the receptor in the postganglionic fibre in the ganglion resulting in stimulation. *(b)* the action is terminated due to destruction of acetylcholine by cholinesterase.

Step 5 is the release of transmitter from the postganglionic fibre. In the case of parasympathetic as well as sympathetic cholinergic fibres (e.g. to sweat glands) this is acetylcholine. In the case of sympathetic fibres this is noradrenaline.

Step 6(a) is the combination of the above transmitter with the receptor situated in the effector organ. This results, finally, in the desired effect. *(b)* The effect is terminated by the destruction of the transmitter by a suitable enzyme — Ch E or amineoxidase.

Parasympathetic or cholinergic receptors: From the above, it is evident that acetylcholine acts on 3 types of receptors: *(a)* In the ganglia, (*Step 3a*) where the action is blocked by *hexamethonium*; *(b)* the smooth and cardiac muscles and secretory organs supplied by parasympathetic postganglionic nerve endings (*6a*) where the action is blocked by *atropine*; and *(c)* the myoneural junction where the action can be blocked by *curare*. The above cholinergic receptors are also called *hexamethonium*, *atropine*, and *curare sensitive receptors*, respectively. The receptors in the ganglia are also called '*nicotinic*' because nicotine can stimulate them. Similarly, *muscarine* can stimulate the receptors in smooth and cardiac muscles and secretory organs — hence they are called *muscarinic*.

Some drugs can stimulate the parasympathetic receptors directly, e.g. acetylcholine, methacholine and pilocarpine; others stimulate the receptors indirectly by inhibiting cholinesterase and thereby preventing the destruction of internally secreted acetyl choline, e.g. prostigmine and D.F.P.

Sympathetic or adrenergic receptors: Stimulation of sympathetic

nerves as well as injection of adrenaline can give rise to a biphasic effect. Some blood vessels are dilated whereas others are constricted. The blood pressure may rise and subsequently fall. Further, these different effects can be selectively blocked by drugs. This suggests the presence of different receptors on which the same transmitter adrenaline or noradrenaline can have different effects. Sympathetic receptors are of 3 types:

- (i) *Alpha receptor*: responsible for vasoconstriction and intestinal relaxation and blocked by Ergot.
- (ii) *Beta receptor*: responsible for bronchodilatation, intestinal relaxation and cardioacceleration and blocked by dichloroisoprenaline (D.C.I.)
- (iii) *Metabolic or (δ) receptor*: responsible for glycogenolysis and hyperlipaemia and blocked by Isopropyl methoxamine.

AUTONOMIC DRUGS

Nature of drugs	Ganglia	Parasympathetic	Sympathetic	Neuromuscular junction
Stimulants or mimetics	Acetylcholine Nicotine Neostigmine	Acetylcholine Physostigmine Neostigmine Pilocarpine	Adrenaline Noradrenaline Other sympathomimetic amines	Neostigmine
Blocking or lytics	Nicotine Quarternary ammonium & methonium compounds	Atropine Atropine substitutes	Ergot Dibenamine Phentolamine Priscoline	Tubocurarine Flaxedil Decamethonium, Succinylcholine

Analysis of Drug Action. The steps on which the autonomic drugs produce their blocking action are detailed below. None of them interferes with the normal synthesis or release of the local hormones;

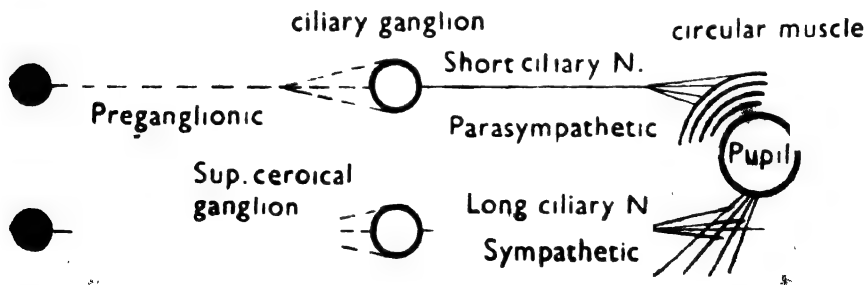
Drug	Steps of action	Result
Acetylcholine	3(a) & 6(a)	Stimulation of ganglia Muscarinic effects
Prostigmine	3(b) & 6(b)	Muscarinic and nicotinic effect. Direct stimulation of skeletal muscles.
Atropine	6(a)	Blocking of muscarinic effect

<i>Drug</i>	<i>Steps of action</i>	<i>Result</i>
Adrenaline	6(a)	Sympathomimetic effect
Ergotoxine	6(a)	Blocking of alpha receptors
D. & I	6(a)	Blocking of β -receptors
Nicotine	3(a)	Small doses stimulate but large doses block the ganglia.
Curare	6(a)	Relaxation of skeletal muscles

Interplay of Actions: Many organs are supplied both by sympathetic as well as parasympathetic fibres — each of these having often diagonally opposite effect. The overall state of functioning of such organs is the resultant of the two opposite actions, e.g. heart rate and pupil, e.g. stimulation of parasympathetic or paralysis of the sympathetic by surgery or sympatholytic drugs will cause bradycardia and pupillary constriction. The opposite will occur after sympathetic stimulation or parasympathetic paralysis.

RECIPROCAL INNERVATION OF IRIS

In the pupil there are 2 sets of muscles — outer radial fibres supplied exclusively by sympathetic nerves. Contraction of these results in pupillary dilatation (*active mydriasis*). The inner set of circular fibre is supplied by parasympathetic nerve and causes constriction of pupil (*active miosis*). Paralysis of parasympathetic system (e.g. after atropine) results in overaction of the radial fibres and *passive mydriasis* results. Similarly, sympathetic paralysis results in *passive miosis*.



Reciprocal Innervation of Iris

From the brief review of the general considerations of the A.N.S., it is apparent that the functioning of the two main components of

this system, is very complex and yet delicately balanced. The complexity is further increased because of the different steps in the A.N.S. activities—peripheral, central, preganglionic & ganglionic, which often differ from one another. There are thus a large number of variables in the integrated activity of the autonomic system and yet the sumtotal of the normal functioning is carried out in a remarkably balanced manner. No wonder therefore that the Pharmacology of A.N.S., is not free from enormous complexities, as will be discussed in the next few Chapters.

CHAPTER

9

PARASYMPATHOMIMETIC DRUGS

THE THREE IMPORTANT GROUPS, MUSCARINIC AND NICOTINIC ACTIONS, REVERSIBLE AND IRREVERSIBLE ANTICHOLINESTRASE AGENTS, THERAPEUTIC STATUS, TOXICOLOGICAL HAZARDS AND SPECIFIC ANTIDOTES FOR THE LATTER.

[These drugs produce the effects of stimulation of parasympathetic nerve endings either by acting directly on the cholinergic receptors or indirectly through the inhibition of cholinestrase, which destroys acetylcholine. The general pattern of action of parasympathomimetic drugs is cholinergic in nature, viz. (a) Miosis, (b) C. V. depression, (c) Plain muscle contraction—bronchioles, intestine, bladder, and (d) Increased glandular secretions; in other words—muscarinic type of action, blocked by atropine.

Of the 3 groups, *choline esters*—which comprise of acetyl choline and other choline derivatives, have limited therapeutic uses excepting that mecholyl and neostigmine are used in paroxysmal auricular tachycardia and urecholine and furmethide, along with neostigmine, in paralytic ileus and urinary retention. Of the *anticholinestrase group*—neostigmine, pyridostigmine and mytilase in myasthenia gravis and the *cholinergic alkaloid*—pilocarpine, along with eserine, in glaucoma.

Some of the irreversible anticholinestrase drugs—DFP, HETP and particularly parathion, malathion and TEPP, used as insecticide, cause 'diazinol poisoning', characterised by the symptom complex of cholinergic responses and treated by atropine, homatropine and also by some of the oximes, the specific reactivators of the enzyme, like 2-PAM, DAM, MINA and TMB-4, with remarkable success.]

These are chemical substances which mimic or imitate the effects of stimulation of the parasympathetic nerve endings. They produce their action either by acting *directly* on the cholinergic receptors or *indirectly* through the inhibition of *cholinestrase*, an enzyme which hydrolyses acetylcholine.

CLASSIFICATION

<i>Choline Esters</i>	<i>Acetylcholine, mecholyl, carbachol, urecholine and furmethide</i>
Inhibitors of cholinestrase	<i>Reversible — Physostigmine, prostigmine, benzpyrinium, pyridostigmine, mytelase and demecarium</i>

Plate X

PLANTS CONTAINING AUTONOMICALLY ACTIVE PRINCIPLES

FIG. 27. *Physostigma venenosum*.

FIG. 28. Poisonous mushrooms.

FIG. 29. *Atropa belladonna*.

FIG. 30. Ergot.

Inhibitors of Cholinesterase

Irreversible — Di-isopropylfluorophosphate (DFP), Tetraethylpyrophosphate (TEPP), Hexaethyl tetraphosphate (HETP), and Octa-methyl pyrophosphoramidate (OMPA)

Cholinergic alkaloids

Pilocarpine, muscarine and arecoline

Parasympathomimetic actions are classified into *two broad groups*, depending on the type of receptors involved in the production of the effects.

Muscarinic Action: Produced by the effect of drugs on the cholinergic receptors supplied by *post ganglionic* cholinergic nerve-endings. It is characterised by a fall in B.P., constriction of pupil, bronchoconstriction, stimulation of intestine and increased secretions. It resembles the actions of muscarine and is blocked by atropine.

Nicotinic Action: Produced by the stimulation of cholinergic receptors, supplied by *preganglionic* fibres and somatic nerves. It is characterised by the stimulation of ganglia and contraction of skeletal muscles. The former is blocked by ganglion blocking agents, while the latter, by curare, a neuromuscular blocking agent. The latter action is known as '*anticurare action*'.

Both these effects are demonstrable on the *intestinal muscle* of the '*primitive tench fish*', having an *outer layer* of striated muscle and an *inner layer* of smooth muscle, both supplied by the vagus nerve. The outer coat responds to the stimulation by a rapid contraction, characteristic of the nicotinic effect of skeletal muscles, while the inner one, by a slow contraction, characteristic of the muscarinic effect of smooth muscles. When the undivided vagus is stimulated, a mixed contraction quick, followed by the slow component of contraction, is obtained. After *curare*, the quick component or nicotinic effect disappears, while after *atropine*, the slow or muscarinic component disappears. When both the drugs are given, no contraction is produced by vagal stimulation, as both the components are blocked.

CHOLINE ESTERS

These are quaternary ammonium compounds, represented by the following structures:

ACETYL CHOLINE

A strong base, with a cationic head and an esteratic site, acting as

Plate XI **TISSUE RESPONSES TO CHOLINOMIMETIC AND** **CHOLINOLYTIC DRUGS**

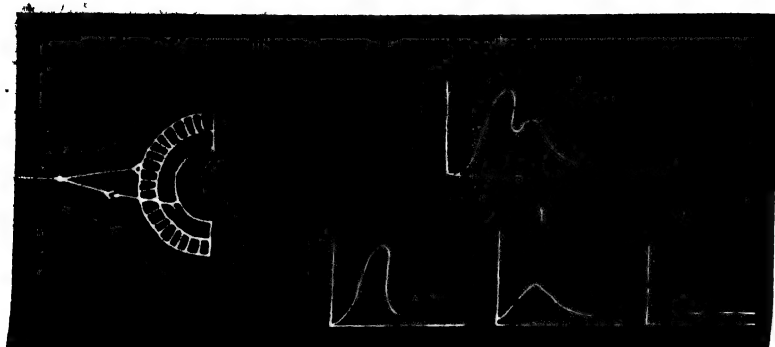


FIG. 31. *Tench fish intestine:* (A) Containing an outer coat of striped muscle (S) which receives motor fibres from vagus (V_1). The inner smooth muscle coat (M) is innervated by postganglionic parasympathetic fibres also coming through vagus.

(B) Stimulation of the nerve results in a twitch (due to 'nicotinic action'; i.e. contraction of the striated muscle) followed by slow sustained contraction phase (smooth muscle contraction; 'muscarinic action').

(C) Atropine abolishes the slow component and

(D) d-tubocurarine abolishes the twitch response.

(E) Simultaneous administration of the two antagonists results in complete blockade of the muscular contractions.

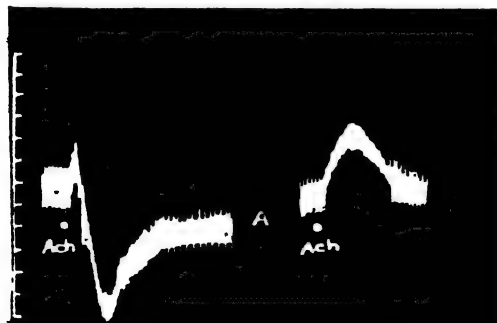
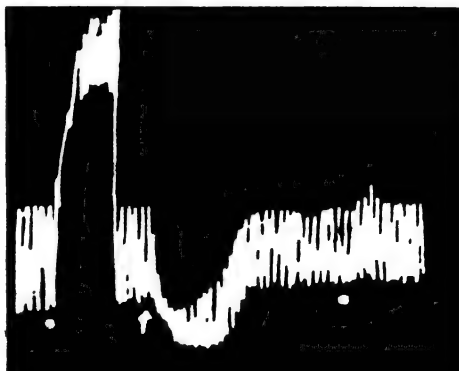
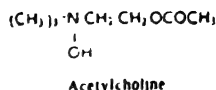
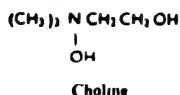


FIG. 32. *Dog blood pressure :* Acetylcholine (ACh) given at (o) caused a prompt but short-lived fall of blood pressure due to cardiac slowing and vasodilatation (muscarinic action). After atropine (A), muscarinic action of ACh. is blocked and rise of blood pressure (nicotinic action) due to ganglionic and adrenal medullary stimulation, occurs.

FIG. 33. *Isolated rabbit ileum :* Acetylcholine given at (o) causes spasm of longitudinal plain muscle. This effect is prevented by prior administration of atropine at (↑). Atropine itself causes slight relaxation of the intestine.



reactive centres. White, crystalline, hygroscopic, water soluble power, used as chloride or bromide salt — *Dose*: 50-200 mg. S.C.



Metabolism : Ineffective orally, as it is readily hydrolysed in the G.I.T. On S.C. administration, it is rapidly destroyed in blood and tissues, by cholinesterase. Less than 3% is excreted in the urine.

Actions : Similar to cholinergic responses, seen earlier, but with exogenous acetyl choline, suprathreshold concentration in the effector cells within a minimal period of time, is necessary, otherwise response may not be elicited.

C. V. system : Fall in B.P. due to peripheral vasodilatation, bradycardia and reduced forces of auricular contraction. In high doses there is *A. V. block*. After prior atropinisation, there may be a rise in B.P., due to stimulation of ganglia and adrenal medulla, causing release of adrenaline and nor-adrenaline. This is known as '*nicotinic action*' of acetyl choline.

G. I. Tract : Increase in tone and motility. In situ — transient spasm, followed by prolonged hypoactivity, due to release of adrenergic activity. (Plate XI; Fig. 33)

Eyes : Constriction of pupil or miosis, only after intraarterial injection and denervation, and not on local instillation. Intraocular tension is raised.

Respiration : Transient stimulation from hypotension, bronchoconstriction and increase in bronchial secretions.

Skeletal muscles : Action on the motor end-plate, causing depolarisation and contraction but no effect on muscle fibres.

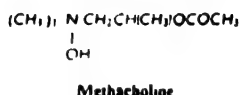
Secretions : Increased.

C. N. System : Spiking activity from direct application to cortical areas. Respiratory, vomiting and vasomotor centres are activated by local application, polysynaptic reflexes, as well as central synaptic transmissions, are facilitated.

Toxicity : Nausea, vomiting, flushing, palpitation, substernal constriction, and profuse perspiration, These are effectively antagonised by atropine sulphate — 1 mg S.C.

Uses: In therapeutic doses, hardly any effect excepting slight fall in B.P., G.I.T. stimulation and muscular fasciculation. Acetyl choline is an important pharmacological tool with hardly any therapeutic use due to transient nature of action.

ACETYL β -METHYL CHOLINE (Mecholyl, Methacholine)



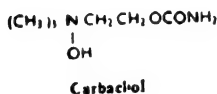
With a view to remove the nicotinic effect of acetyl choline for prolonging muscarinic effect, many compounds were synthesised, of which, *Mecholyl* only is of therapeutic value.

It differs from acetylcholine by having (a) An additional methyl-group on carbon, beta to the quaternary nitrogen, (b) Oral effectivity, (c) Only muscarinic action, (d) Action prolonged, as destroyed by true cholinesterase only, (e) Increased gastric juice secretion, rich in acid.

Preparation and Dose: *Mecholyl chloride* — Capsules of 200 mg. *Injection* — 10 mg/cc. *Mecholyl bromide* — Less hygroscopic, *Tablets* of 200 mg. **Doses:** Oral 50-600 mg; S.C. 2.5-50 mg.

Uses: (a) Paroxysmal auricular tachycardia. (b) Post-operative urinary retention and for inducing evacuation of bladder in patients with cord injury and tabes dorsalis. (c) Peripheral vascular diseases — doubtful value.

CARBAMINOYL CHOLINE (carbachol, doryl)



It is a carbamic acid ester of choline, and more stable than acetylcholine. Its action is gradual and prolonged, as it is not destroyed by cholinesterase. Because of this, it is one of the most toxic choline derivatives.

Preparation and Dose: Carbaminoyl choline chloride — 0.2 to 0.8 mg S.C. or orally.

Actions : Resembles acetylcholine, having both muscarinic and nicotinic actions. Effect on urinary bladder and G.I.T. more marked than on the C.V.S. Like mecholyl, gastric secretion is increased.

Uses : Due to toxicity, its use in urinary retention and post operative paralytic ileus has been completely abandoned.

URECHOLINE (Bethanechol)

A carbamic acid ester of β -methyl choline, refractory to destruction by cholinesterase, exhibiting only muscarinic action. Urecholine chloride — *Tablets* — 5 mg; *Injection* — 5 mg/ml.

Dose: *Oral*—10—30 mg t.d.s.; *S.C.*—5 mg.

Actions: Resembles mecholyl, but the effects are more prolonged. It possesses muscarinic action of mecholyl and stability of carbachol.

Uses: (a) Post operative urinary retention (b) Megacolon (c) Adynamic ileus.

FURMETHIDE (Furthrethoenium)

It exhibits pharmacological effects of mecholyl with a specific effect on the *urinary bladder*. *Furmethide Iodide*—25 mg/Os; 5 mg/S.C.

Use: Urinary retention.

COMPARATIVE TABLE

	<i>Ach</i>	<i>Mecholyl</i>	<i>Carbachol</i>	<i>Urecholine</i>	<i>Furmi- thide</i>
Nicotinic effect	+	—	++	—	+
Hydrolysis by ChE-	++	+			
True—	+	+	—	—	—
Pseudo—	+	—			
Duration of action	+	++	+++	++	+
Plain muscle	+	++	++	+	+
C. V. Effect	+	++	+	+	—

CHOLINESTERASE INHIBITORS

These drugs produce parasympathomimetic effects by inhibiting cholinesterase, thus sparing acetylcholine from enzymatic hydrolysis.

Cholinesterase: A family of enzymes, which hydrolyses choline esters. They are of two types:

(a) *True or Specific or Acetyl cholinesterase*: found in grey matter, cholinergic nerve terminals and in R.B.C. It hydrolyses acetylcholine *in vivo*, which is the preferred, if not the only substrate. It also hydrolyses mecholyl, but not benzoyl choline.

(b) *Pseudo or non-specific cholinesterase*: found in plasma, white matter and liver. It hydrolyses acetylcholine *in vitro* and also butyryl choline. The latter is more rapidly affected than acetylcholine and benzoyl choline. It does not hydrolyse mecholyl.

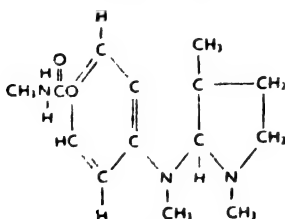
Hydrolysis of acetylcholine takes place in three steps: (a) *absorption* of the substrate on the enzyme, (b) *acetylation* of the enzyme and (c) *hydrolysis* to acetic acid and choline.

Acetylcholine possesses a cationic head $-(CH_3)_3N^+-$, a two-carbon chain $-CH_2-CH_2-$ which links cationic head with the ester group in $-O.C_4H_9$. Cationic head is adsorbed on the anionic site of cholinesterase, while the ester group, on the esteratic site.

The activity and the potency of the inhibitor is related to the *stability* of the *enzyme-inhibitor complex*. In cases where the enzyme slowly hydrolyses the inhibitor, the inhibition is *reversible*, e.g. Eserine, while in those cases where the enzyme is phosphorylated and the inhibitor cannot be hydrolysed, *irreversible* inhibition of the enzyme occurs, e.g. D.F.P.

Effects of cholinesterase inhibition are largely due to accumulation of acetylcholine, producing the following three components of action—*muscarinic effects*—as referred earlier, *nicotinic effects*—muscular twitchings, followed by weakness and *central effects*—restlessness, dizziness, tremors, hallucinations, coma and convulsions. These effects are more marked with lipid soluble organo phosphorus compounds.

PHYSOSTIGMINE



Physostigmine

Also known as *eserine*, it is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum*—calabar bean, ordeal poison, (Plate X;

Fig. 27). It is a tertiary amine and the salt, *eserine salicylate* is colourless, bitter and soluble in water. The solution is unstable and becomes pink on standing due to the formation of '*Rubreserine*' or *eseroline*, which can be prevented by using water saturated with CO_2 for preparing the solution.

Metabolism: Readily absorbed from the G.I.T., as well as from the mucous membrane of cornea, widely distributed in the body, partly destroyed and partly excreted unchanged, mainly through urine and only small quantities are excreted in saliva and bile.

Dosage Forms: (a) *Eserine salicylate*—2 mg/Os, 0.5—1 mg. S. C. (b) Ophthalmological solution — 0.1 to 1%. (c) *Lamella* — containing 0.065 mg for ophthalmic use.

Actions: Though resembling acetylcholine in general, the important actions are on the smooth muscles, eye and skeletal muscles.

G. I. Tract: Tone and motility are increased and there may be evacuation of bowel.

Eye: After local instillation or injection, miosis with spasm of accommodation. Action starts in 2-5 mts, maximum in 1-2 hours and lasts for 12 to 36 hours. Even after maximum miosis, the light reflex persists. Miosis causes widening of the angle and facilitates drainage of aqueous humor through the *canal of Schlemm*, resulting in a fall in I.O. tension, which is more marked in *glaucoma*.

Skeletal Muscles: No direct effect, but increased tone and contraction of skeletal muscles from inhibition of cholinesterase.

C. V. S: fall in B.P., and bradycardia. In large doses, direct depression of myocardium.

Toxicity: Accidental or homicidal—Symptoms resemble ACh: (a) A.V. block, (b) muscular weakness, (c) blurred consciousness, and (d) difficulty in breathing which are treated by the *physiological antidote*—atropine sulfate—1-2 mg. S.C. It combats all the symptoms except muscular twitchings, which disappear after sometime.

NEOSTIGMINE (PROSTIGMINE)

A synthetic quaternary ammonium compound, bitter and freely soluble in water. It acts as a reversible cholinesterase inhibitor, as well as acetylcholine analogue, with short duration of action.



Neostigmine

Metabolism: Poorly absorbed, exact fate unknown; a small quantity, excreted unchanged in the urine.

Dosage Forms: Neostigmine bromide—*Tablets* of 15 and 30 mg.—15 mg/os; *ophthalmic solution*—5%.

Neostigmine methyl sulfate—*ampoules*—1 cc. containing 0.25, or 1 mg/cc. *Dose:*—0.5 mg. S.C. or I.M.

Actions: Resemble other cholinergic drugs with both muscarinic and nicotinic effects, the most important one being on the *skeletal muscles*—increase in tone and contraction by (a) a direct stimulant effect on the neuromuscular apparatus, (b) indirectly through inhibition of cholinesterase.

Uses: (a) Diagnosis and treatment of *myasthenia gravis*. (b) Post operative *intestinal atony* and *urinary retention*. (c) As a *miotic* in *glaucoma*. (d) *Paroxysmal auricular tachycardia*. (e) *Curare poisoning*. Though highly effective, due to its prolonged action and side effects *Tensilon* is preferred.

Pyridostigmine bromide (Mestinon bromide): an analogue of neostigmine, but less potent, less toxic and longer acting with a higher margin of safety. It is available as 60 mg. *tablets*, average daily dose—600 mg, in *myasthenia gravis*. *Mytelase chloride*: A potent inactivator of cholinesterase, which is more active against true than pseudo ChE. It is more potent than neostigmine with a longer duration of action. *Tablets* of 25 mg; 75—150 mg/day in *myasthenia gravis*. *Benzpyrinium bromide*: A drug chemically related to neostigmine and acting chiefly through inhibition of ChE. *Ampoules* of 0.5 mg/cc. used in post operative *intestinal atony* and *urinary retention*. *Demecarium bromide*: A powerful ChE inhibitor with sustained action and sometimes used in *resistant glaucoma*, as 0.25% solution.

IRREVERSIBLE CHOLINESTRASE INHIBITORS

These are the organophosphorus compounds, which produce an irreversible inhibition of cholinesterase. They are not specific inhibitors of cholinesterase but inhibit a broader group of enzymes, viz. carboxylic esterases (trypsin, chymotrypsin and lipases). Their action takes place in two stages: *Stage I*—reversible — formation of 'enzyme-inhibitor-complex'. *Stage II*—irreversible phosphorylation of the enzyme and formation of reaction products.

Enzyme phosphate, unlike enzyme acetate, is very stable and is hydrolysed very slowly with the result that the effect of these compounds is extremely prolonged.

Di-Isopropylfluorophosphate (D.F.P.): Colourless oily liquid, with peppermint like odour, sparingly soluble in water but readily in oils. It undergoes hydrolysis in alkaline medium and is rendered inactive.

Metabolism: It is absorbed from the G.I.T. and from sites of injections. In the body, it undergoes rapid enzymatic hydrolysis and the resulting product—*di isopropyl phosphoric acid*, is pharmacologically inactive. Although the sojourn of D.F.P. in the blood is brief, its effects on the organisms are lasting.

Actions: Affinity of DFP, for non-specific esterases is greater than the affinity for specific cholinesterase. Its actions are similar to those produced by the other anticholinesterase drugs and differ only in persistence. Recovery depends on the rate of the regeneration of ChE in the tissues affected. Its effect on the neuromuscular junction is not as prominent as with neostigmine or physostigmine, because of the limited water solubility, which impairs its access to this site.

It is used in *resistant glaucoma*—0.01 to 0.2 mg/cc. of peanut oil, one instillation per day, effect lasting for 2-3 weeks, but may be irritant.

Tetraethyl Pyrophosphate (TEPP): Colourless liquid, miscible with water but the aqueous solution is unstable. Solution in peanut oil or propylene glycol is stable.

Metabolism and Actions: It is absorbed from the G.I. tract and is readily hydrolysed by enzymes present in the liver to inactive phosphoric acid derivatives.

Because of water solubility, it reaches the neuromuscular junction easily and produces effects there more readily than DFP. It differs from DFP in the following respects: (a) Onset of action is rapid but the effects are transient, (b) Nicotinic effects more pronounced, (c) Less effects on the C.N.S., and (d) is more potent than DFP as ChE inhibitor. It is seldom used as it has no advantage over other drugs in the treatment of myasthenia gravis and glaucoma.

Hexaethyl Tetraphosphate (Hetp) : A viscous, brownish coloured liquid, miscible with water, the solution is unstable. It releases TEPP as its active principles, with which, it resembles in actions and uses. *Phospholine Iodide*—another long acting ChE inhibitor, is sometimes tried in glaucoma, in a concentration of 0.06—0.25% but only in resistant cases, not responding to other miotics.

Diazinol Poisoning: Of late, a number of insecticides of this series—Parathion, Malathion, TEPP—are causing serious toxic manifestations after accidental or suicidal uses. The symptoms of poisoning are attributed to a large measure, to the irreversible inhibition of ChE and recovery depends on the restoration to normal activity of inhibited enzyme or regeneration of new ones.

The *symptom complex* refers particularly to: (a) Miosis, frontal headache, anorexia, nausea, vomiting, abdominal cramps and diarrhoea. (b) Increased nasal, bronchial and sweat secretions. (c) Tightness of chest with bronchoconstriction and dyspnoea. (d) Muscular twitchings, cramps and weakness. (e) Giddiness, anxiety, ataxia, convulsions and coma. (f) Depression of C.V and respiratory centres, fall of B.P., cyanosis and death.

Treatment comprises of palliative and curative measures: (a) Removal from the environment, decontamination, maintenance of patent airways and artificial respiration. (b) *Atropine*—2 mg. I.M., every 3-5 minutes to a total not exceeding 100 amps. or signs of atropinisation occur. It blocks muscarinic effect but does not improve weakened or paralysed respiratory musculature. (c) Local ocular effects are treated by *homatropine*—2% or atropine—0.5% solution or ointment.

REACTIVATION OF THE ENZYME BY OXIMES

A number of oximes and hydroxamic acids are capable of reactivating cholinesterase inhibited by organophosphorus compounds. These are (i) 2-pyridinealdoxime methochloride (2-PAM), (ii) Diacetyl

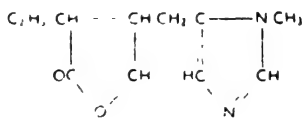
monoxime (DAM), (iii) Mono-isonitrosoacetone (MINA), (d) TMB-4.

The drug of choice is 2-PAM, which is used as 2-PAM chloride or 2-PAM (P_2S) methanesulfonate salt. It is a white to off-white, odourless, non-hygroscopic, crystalline powder, soluble in water. It is stored as crystalline or lyophilized powder in vials of 1 and 5 Gm.

Mechanism of Action: The exact mechanism of action is not known but it is suggested that the effect occurs in two steps: (i) Formation of a complex between oximate ion and phosphorylate enzyme. (ii) Liberation of phosphorylated oxime and regeneration of enzyme activity.

Dosages: 2.5 Gm. of PAM chloride I.V. slowly over a period of not less than 15 mts. Thereafter 1.25 Gm is repeated every 30 mts, till muscle strength is increased significantly.

CHOLINERGIC ALKALOIDS



Pilocarpine

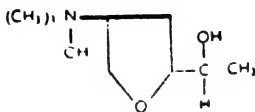
PILOCARPINE: It is an alkaloid obtained from the leaves of *Pilocarpus jaborandi*. It possesses only muscarinic effects, the important actions being on (a) Secretions and (1) Eye—principally

Marked increase in secretions particularly salivary and sweat secretions. A dose of 10-15 mg in man, results in the secretion of 2-3 liters of sweat, containing electrolytes and urea.

Local instillation into the eye causes pupillary constriction, spasm of accommodation and a brief initial rise in intraocular pressure, followed by a fall.

Preparations: Pilocarpine nitrate or hydrochloride—0.25 to 2% ophthalmic solution.

Uses: (a) as a miotic in glaucoma, and (b) to counteract atropine mydriasis.



Muscarine

MUSCARINE: An alkaloid obtained from mushroom—*Amanita muscaria* (Plate X; Fig. 28). It is a quaternary ammonium compound, but like acetyl-choline it is not an ester. It possesses muscarinic action and is important only from the point of toxicity.

Mushroom Poisoning: It results from ingestion of sufficient amounts of *A. muscaria* or *A. Phalloides*. Poisoning with the latter is rare but more serious and differs from the former in that the onset of symptoms is delayed for several hours after ingestion and is not affected by atropine but by antitoxic serum and routine treatment of dehydration.

Symptoms: salivation, lachrymation, gastroenteritis with nausea, vomiting, bloody diarrhoea, bradycardia, prostration, shock and terminal convulsions.

Treatment: (a) Gastric lavage, (b) Correction and maintenance of fluid and electrolyte balance. (c) Atropine to combat muscarinic effects.

Arecoline: An alkaloid from *Areca catechu*, closely related to pilocarpine, both in chemical structure and pharmacological activity. It is not used therapeutically.

CLINICAL APPLICATIONS

<i>Paroxysmal tachycardia</i>	<i>Glaucoma</i>	<i>Myasthenia gravis</i>	<i>Paralytic ileus and urinary retention</i>
Mecholyl	Pilocarpine	Neostigmine	Neostigmine
Neostigmine	Physostigmine	Pyridostigmine	Benzpyrinium
	DFP	Mytelase	Urecholine
	Demecarium		Furmithide

THERAPEUTIC CONSIDERATIONS

Several, of which, the following deserve special considerations:

Paroxysmal Auricular Tachycardia: Characterised by repeated, paroxysmal attacks of tachycardia with sudden onset and termination, the auricular rate being between 150-220/minute. The paroxysms may last for a few minutes, upto a few days and may recur, periodically or with great frequency. Although it may occur at any age or sex, patients with mitral stenosis, hyperthyroidism and auricular septal defect, are more commonly affected.

Drugs are indicated, when simple measures like holding of breath, drinking ice-cold water, self-induced vomiting, etc. fail.

Quinidine: 0.3 Gm with *Phenobarbitone* 60 mg is tried first. Cholinergic drugs, because of unpleasant side effects, are tried, when the above measures have failed. *Mecholyl* 10-20 mg S.C. or *Prostigmine*—1 mg I.M. are useful as palliatives and not preventive, for which latter, *Quinidine* is the drug of choice.

Glaucoma: An ocular condition, characterised by an increase in intra-ocular tension due to: (i) increased hydrostatic pressure in ocular capillaries, resulting in increased formation of aqueous humor from ciliary processes or (ii) increase in protein content of the aqueous humor or (iii) an obstruction to the circulation of the aqueous humor in the pupil or to its drainage at the angle of eye—canal of Schlemm. It may be *primary* or *secondary*.

Miotics are of value in *closed-angle type of primary glaucoma*, where the essential lesion is a closure of the angle of the anterior chamber due to a capillary stasis, associated with increased permeability, leading to oedema of the tissues of the eye. They are also of value in the early stages of primary glaucoma of the simple type.

Acute glaucoma: A painful condition necessitating immediate relief. The therapy comprises of the use of: (a) Miotics, and (b) Analgesics, *Prodromal stage*—Pilocarpine 0.5—2% or Eserine 0.25—1%, 3 or 4 times a day.

During attack: (a) Eserine 1—2% combined with 2% pilocarpine/ every 5 mts for $\frac{1}{2}$ hour, then $\frac{1}{2}$ hourly, till persistent miosis, (b) Analgesics to relieve pain, (c) Diamox 2 tab. stat, 1 tab. 6 hourly.

Chronic glaucoma: (a) Pilocarpine—2%, 3 or 4 times a day, (b) Diamox —1 tab. 6 hourly, (c) In cases of failure, DFP may be tried.

Myasthenia Gravis: A serious condition of chronic nature involving neuromuscular junction and characterised by weakness, ptosis, blurred vision, diplopia, difficulty in swallowing and talking. Head and neck muscles are commonly involved, the order of paralysis being—levator palpebri superioris→face and neck muscles,→muscles of the limbs→intercostal muscles and diaphragm. The disease may remain static or it may progress until involvement of respiratory muscles occurs, which, along with some intercurrent disease, is the cause of death.

Pathogenesis: The disease is caused by a defect in the neuromuscular transmission in affected muscles, due to: (a) Decreased release of acetylcholine at the motor nerve endings, (b) Increased cholinesterase activity in the affected muscles, (c) Presence of a curare like substance,

circulating in the body, (d) An abnormal end-plate or potassium shift in the muscle.

Neostigmine: alone or in combination with *ephedrine*, is very valuable in the management of this disorder, its value depending on (a) its ability to inhibit cholinesterase, (b) direct stimulant effect on the neuromuscular apparatus, (c) a shift of muscle potassium to produce a corresponding increase in blood potassium.

The dose has to be individualised. It is better to start with a smaller dose, gradually increasing it till optimal results are achieved. *Average dose*: 0.5 to 1 mg. S.C. or I.M. 15 mg. 3 to 6 times a day—orally. As tolerance develops, the dose may be increased to 30 mg. 3-6 times a day.

Results: a good palliative with demonstrative effect, lasting for 4-6 hours but the inexorable course of the disease cannot be checked. The drug can also be used as a diagnostic agent in suspected cases of myasthenia gravis.

In cases, which have become resistant to neostigmine, *mestinon bromide*—600 mg/day or *mytelase chloride*—75-150 mg/day, may be tried.

Paralytic Ileus and Atony of Bladder: Post-operative or otherwise, some of the choline esters and anticholinesterase drugs find their application in preventive and curative therapies.

Carbachol—0.25 mg. I.M. is the drug of choice for *bladder, atony* while for *Paralytic ileus*—prostigmine and doryl are used.

CHAPTER

10

PARASYMPATHETIC BLOCKING AGENTS

THE SOLANACEAE FAMILY—ATROPINE, HYOSCINE AND
ATROPINE SUBSTITUTES — MYDRIATIC, ANTISPASMODIC,
ANTISECRETORY AND ANTIPARKINSONIAN DRUGS.

[This group of drugs which block cholinergic responses at the parasympathetic effector cells (muscarinic effect), is also known as parasympatholytic drugs. They comprise of 2 principal solanaceae alkaloids—atropine and scopolamine and a number of derivatives and substitutes. Of the two alkaloids, atropine combines a typical peripheral parasympatholytic effect along with central stimulant action, while hyoscine hydrobromide is a depressant and sedative of the central nervous system.

The main action of *atropine* comprises of: (a) Passive mydriasis with cycloplegia, (b) Antispasmodic effect on all smooth muscles, and (c) Anhydrotic effect on all secretions. These actions are therapeutically exploited in—respiratory depression, vagal syncope, preanaesthetic medication, intestinal, biliary and renal colics, asthma, excessive perspiration, hypercholrhydria and treatment of anticholinestrase poisoning. *Hyoscine hydrobromide* has much more limited uses excepting in hyperexcitable states, Parkinson's disease, preanaesthetic sedation, twilight sleep and motion sickness.

Atropine substitutes and derivatives have been synthesised for removing the unwanted side-effects of atropine in cases where one of the principal actions only is to be utilised.

Thus *homatropine hydrobromide* belonging to the mydriatic group has the advantage of shorter duration of action than atropine and is thus preferred as a mydriatic in ophthalmology for refraction purposes. *Novatropine*, *trosetine* and *pavatrine* show predominantly antispasmodic effect without causing mydriasis and are used in biliary and other types of colic pains. *Banthine*, and *probanthine*, possess antisecretory and antispasmodic actions and are used in pylorospasm and gastric hyperacidity. Similarly, *artane*, *benzatropine*, *parsidole* and sometimes *hyoscine hydrobromide*, *chlorpromazines* and *dexedrine* are used for combatting various symptoms of Parkinson's disease—rigidity, tremor, salivation, lethargy, as palliative measures.]

A group of alkaloids, obtained from the Solanaceae family of plants, comprising of (a) *Atropa belladonna*, (b) *Hyoscyamus niger*, and (c) *Datura stramonium*, which block the effect of parasympathomimetic drugs on the receptors, supplied by post ganglionic cholinergic nerve

Plate XII

STRUCTURE OF ANTICHOLINERGIC DRUGS

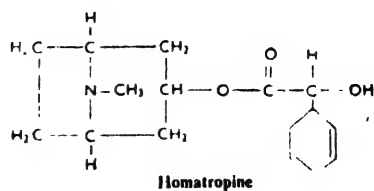
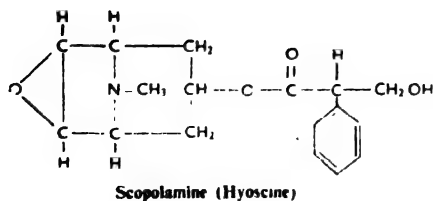
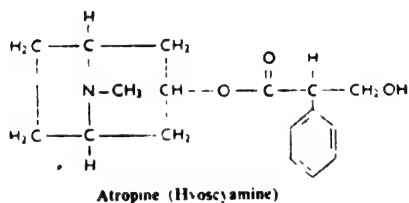
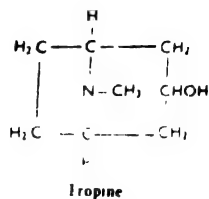
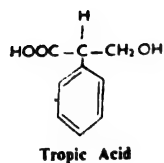


FIG. 34. Tropic acid, Tropine, Atropine, Scopolamine and Homatropine.

endings and are also known as parasympatholytic agents, with varying degrees of central effect.

The important *active principles* are:

- (a) Atropine or dl-hyoscyamine,
- (b) dl-hyoscyne or scopolamine,
- (c) l-hyoscyne.

Their chemical nature is shown in Plate XII, Fig. 34.

ATROPA BELLADONNA

Popularly known as '*Deadly night shade*', the word *Atropa*, in Greek mythology, refers to 'Cutting the thread of life' and *Belladonna*—'the beautiful lady'—a name given to the plant because of its mydriatic effect. It is a perinneal plant, about a meter in height. Both leaves and roots are used for the preparation of drugs. Most of the belladonna actions are, however, contained in leaves, which are usually 2.5—5 cm. in length. (Plate X; Fig. 29).

Atropine, a racemic compound, is not present as such in the plant, but is possibly formed during the process of extraction. Chemically, it is an ester of tropic acid with tropanol, the tropic acid radical, being responsible for the pharmacological activity. (Plate XII).

Dosage-Forms: Many and prepared both from leaves and roots of the plant—powder, tincture, extract, liniment, plaster, lamella, oculentum and injection: (a) Tincture belladonna—0.3—2 ml. (b) Atropine sulphate—0.25—1 mg. Tablets—0.5 mg. Injection—0.6 mg/ml; Solution—0.5—1. %; Ointment—1 %.

Mechanism of Action: (a) Atropine does not interfere with the synthesis, release or destruction of acetylcholine. (b) It combines reversibly with the receptors, with which Ach normally attaches itself, thus preventing the molecules of Ach from exerting their action. This is what is known as—'*end-organ competition*', (c) This competition is explainable by the presence of the nitrogen atom and the ester linkage in atropine at approximately the same distance as between quaternary nitrogen and ester linkage of Ach. (d) Quaternisation of N atom endows increased potency and ability to block nicotinic effects of Ach.

In general, the muscarinic effects of Ach are more easily and completely blocked than are the effects of parasympathetic nerve stimulation, but the relative susceptibility of various organs and tissues differs.

Metabolism: (a) It is completely absorbed after oral or parenteral

administration and also after local instillation in eye, (b) It rapidly disappears from the blood and is destroyed in the liver by enzymatic hydrolysis, (c) Only 1/3rd is excreted unchanged in urine, the rest as degradation products, (d) Small quantities are also excreted in the milk.

Actions: Essentially two: (a) Stimulation of C.N.S.—cortical and medullary centres, and (b) Parasympatholytic effect referring particularly to eyes, C. V. system, smooth muscles of respiratory, alimentary and urinary tracts. All secretions are decreased.

C.N.S.: (a) There is hardly any effect in therapeutic doses, but in larger doses, stimulation of sensory and motor cortex, spinal cord and respiratory centre. After repeated administration, depression from exhaustion, may occur (b) It relieves muscular stiffness in parkinsonism and prevents motion sickness by obscure effects on the C.N.S.

Eye: (a) Circular muscle fibres of the iris, which constrict the pupil, are innervated by cholinergic fibres from the IIIrd nerve. The same nerve also supplies ciliary muscle, responsible for the movements of the suspensory ligaments, thus regulating the convexity of the lens, (b) Atropine blocks the effect of Ach at both these sites, causing *passive mydriasis*, *cycloplegia* and a rise in intraocular pressure. Mydriasis is due to unopposed action of the radial muscle fibres, while loss of accommodation is due to paralysis of ciliary muscle, (c) These effects are produced on local applications. Mydriatic action starts in 15-30 mts, is maximum in 2-3 hours and lasts for 3-7 days, while cycloplegia starts in 30-60 minutes and lasts for 48 hours.

C.V.S.: (a) From small doses, there is bradycardia due to stimulation of cardio-inhibitory centre in the medulla and from large doses, tachycardia from blocking of vagus peripherally, (b) With therapeutic doses, hardly any effect on B.P., but from larger doses, mild rise due to stimulation of vasoconstrictor centre and tachycardia. (c) With still larger doses, fall in B.P. from peripheral vasodilatation, depression of the vasoconstrictor centre and ganglionic blockade, may occur.

Smooth muscles—Alimentary tract—main action is on stomach and small intestine and both secretory and motor functions are affected. It reduces tone and motility and relieves pylorospasm. It also depresses nervous phase of gastric secretion and volume more than the acidity is diminished. **Biliary tract**—relaxation, with little effect on bile secretion. **Respiratory tract**—secretions of nose, pharynx and bronchii are reduced, and bronchial muscles are relaxed. **Urinary tract**—relaxation of ureter and detrusor muscle, but increase in tone of vesical sphincter. It is therefore useful in cases of enuresis or wetting of bed in children.

Secretions—*Sweat and salivary secretions are reduced, causing dryness of skin and mouth. Secretory response to cholinergic drugs or chorda tympanii stimulation, is blocked. Pancreatic secretion, induced by pilocarpine or vagal stimulation, is blocked but secretory response to secretion is not altered.*

Miscellaneous: On local application to inflamed areas, mild anodyne action from depression of sensory nerve endings, is produced.

Poisoning Effects: Accidental, suicidal or homicidal but not very frequent. (a) Dry, flushed and red hot skin, parched lips, mydriasis, (b) Peculiar delirium, hallucinations, incoordination and stupor. A drop of urine put on the cat's eye producing mydriasis, may clinch the diagnosis.

Treatment: (a) Gastric lavage with KMnO_4 solution, for oxidising the alkaloids, (b) Barbiturate as sedative, and (c) Pilocarpine as antidote.

Uses: *Externally:* plaster and liniment as local anodyne and counter irritant for sprain, inflammation and engorgement of breast. Use almost discarded now.

Internally: (a) Respiratory depression, vagal syncope and preanaesthetic medication, (b) Intestinal, biliary and renal colics — often combined with morphia. (c) Enuresis, excessive perspiration and hyperchlorhydria. (d) Mydriatic use when complete cycloplegia is needed. (e) Treatment of poisoning with anticholinestrase drugs and poisonous mushrooms.

HYOSCYAMUS NIGER

Popularly known as 'Henbane', the *folia*, containing 0.05% hyoscyne and hyoscyamine, is official.

Preparations: Tincture—2-4 ml. Hyoscyne hydrobromide—0.3-0.6 mg S.C. Oculentum—0.25% for eye.

Actions: (a) *Peripheral actions*—almost same as of atropine. (b) *Central action*—different. (i) Universal depression of cortex and cord; its sedative effect is opposite of atropine, enhanced by morphia and is used together for "twilight sleep". (ii) Scopolamine doubles the chronaxy of flexor muscles, producing isochronism and relieving spasticity in Parkinson's disease. The effect is of central origin.

Uses: (a) General sedative in hyperexcitable states and psychiatric disorders. (b) Parkinson's disease—1 mg. 2-3 times/day. (c) Preanaesthetic sedation and "*twilight sleep*"—scopolamine —0.6 mg+morphine 15 mg. (d) Motion sickness.

DATURA STRAMONIUM

Dried leaves, flowering tops and seeds, contain the same active principles.

Tinctures and *Extracts* have been in use in the past, as bronchial antispasmodics, but they have completely lost their use in bronchial asthma.

The seeds of *D. alba* mixed with food, produce the same type of poisoning effect as with belladonna, but a type of peculiar delirium and hyperexcitability, are more characteristic of this poisoning.

ATROPINE DERIVATIVES AND SUBSTITUTES

These are synthetic compounds, either derived from atropine or of different chemical nature, having similar action. The underlying idea of bringing these compounds to use is to split the important actions of atropine into 4 different categories: (a) *Mydriatic*, (b) *Antispasmodic*, (c) *Antisecretory*, and (d) *Antiparkinsonian*—each with reduced toxicity and side-effects. The attempt has been partially successful only.

MYDRIATIC GROUP

Homatropine Hydrobromide: (a) An ester of *tropine* with mandelic acid. White, crystalline powder, solubility—1 in 6. *Dose:* 0.5—1 mg (b) It is weaker, less toxic and with only 1/10th. vagal effect of atropine, (c) 1-2% Solution or Lamellae, used solely for mydriatic effect, which is of brief duration.

Euphthalmine (Eucatropine Hcl): (a) An ester of mandelic acid with hydroxytetramethyl piperidine. (b) Weaker and more transient in action than homatropine, the mydriatic effect is rapid and short-lived (24 hours) and with incomplete cycloplegia. (c) 5 or 10% solution is used for simple ophthalmoscopic examinations.

Eumydrine (Atropine methyl nitrate): A quaternary derivative of atropine, exhibiting parasympathetic and ganglion blocking effects

but little or no stimulant action on the C.N.S. The mydriatic effect is rapid and of short duration.

Use (i) As mydriatic—0.5—1 % sol., and (ii) Congenital hypertrophic pyloric stenosis—0.2-0.4 mg/os; 6 times a day, before feeding.

ANTISPASMODIC GROUP

They relieve spasms of the smooth muscles by anticholinergic and direct musculotropic actions.

Syntropan: (*Amprotopine phosphate*): It has weaker cholinergic blocking but stronger musculotropic antispasmodic effect than atropine. *Dose*—50 or 100 mg/os/t.d.s. and 10 mg S.C. in colonic spasticity and dysmenorrhoea.

Amethone Hydrochloride: (a) Anticholinergic, antihistaminic and local anaesthetic actions, in addition to a strong musculotropic spasmolytic effect, (b) It is used as urinary tract antispasmodic. in doses of 50 or 100 mg/os or I.M. 3 or 4 times a day.

Dibutoline: (Iodide or sulphate): (a) A strong anticholinergic and directly acting antispasmodic drug, (b) It is used in doses of 10-40 mg/os or S.C..3 -6 times a day, (c) It also acts as a short acting mydriatic, in 5-10 % concentration.

Trasentine: (*Adiphenine HCl*): (a) An antispasmodic with more musculotropic than anticholinergic effect, it also possesses local anaesthetic activity, (b) *Dose*—75-150 mg/os. t.d.s. or 50 mg. I.M. (c) It is used as antispasmodic for intestinal, urinary and biliary colic and also in dysmenorrhoea.

Novatropine (*Homatropine methyl bromide*): (a) Quaternary derivative of homatropine—a less toxic and weaker parasympatholytic but stronger ganglionic blocking agent. (b) It is used in peptic ulcer, pylorospasm and colonic spasticity, in doses of 2.5—5 mg/os/t.d.s.

Pavatrine HCl—125—150 mg/os/t.d.s. It produces musculotropic and neurotropic relaxation of smooth muscles. *Uses*: same as of trasentine. *Methylscopolamine* (Pamine bromide—2.5 mg t.d.s. A quaternary derivative of scopolamine, lacking central sedative effect.

Dactil (Piperidolate HCl): 50 mg capsules, 4 caps/day. Used to relieve spasm of duodenal and biliary tracts.

ANTISECRETORY GROUP

Banthine (*Methantheline bromide*): (a) A quaternary ammonium compound producing blockades at postganglionic, ganglionic and neuromuscular sites, (b) Tablets of 50 mg (1-2 tabs. q.d.s.) or Ampoules—50 mg/5 ml. Used in Peptic ulcer and chronic gastritis.

Probanthine (*Propantheline bromide*): Tablets of 15 mg. and ampoules of 30 mg, used in peptic ulcer, 1-2 tabs. t.d.s. with meals. It is 2-5 times more potent but less toxic than banthine.

Antrenyl (*Oxyphenonium bromide*): An effective antispasmodic and antisecretory drug, as potent as atropine, but with longer duration of action. It is used in peptic ulcer, hyperacidity, pylorospasm and spasm of the gut: *Dose*: 5-15 mg/os q.d.s.

Other anti-secretory drugs, used in peptic ulcer, are:

Prantal—100-400 mg/os q.d.s. *Drastine bromide*—100-200 mg. q.d.s., *Piptal*—5-10 mg. q.d.s. *Monodral*—5 mg. tabs.

ANTIPARKINSONIAN AGENTS

These drugs are used in the treatment of Parkinsonism or Paralysis agitans, a post encephalitic or arteriosclerotic condition, in which, the basal ganglia are affected. It occurs in late forties and is characterised by *rigidity* of muscles, *tremors*, pill rolling movements of fingers, *mask like* face, salivation and a characteristic *gait*. There are gross degenerative changes in corpus striatum, certain parts of cortex, mid brain and extrapyramidal tract. The disease has a progressive course and all that can be done is to either arrest the progress or to partially ameliorate the troubles, making life more bearable. Various drugs have been used in therapy from time to time and recently a number of synthetic drugs have been discovered for this condition.

Drugs used in this condition, aim at: (a) Controlling rigidity, (b) Combatting muscular tremors, (c) Preventing complications like oculogyric crisis, and (d) Elevating mood of the patient and combating akinesia and lethargy.

Atropine and Hyoscine: (a) Beneficial effects of these drugs are probably due to their central anticholinergic action. *Dose*: Atropine sulphate—1 mg. tab., gradually increased to 3 mg. t.d.s., as tolerance develops. (b) If the patient is excitable and nervous, *Hyoscine*, due to its central depressant and antiparkinsonian action, is used in doses of 0.3—0.6 mg. tabs.

Benztropine Methane Sulfonate (Cogentin): (a) White, crystalline, water soluble powder. (b) Exhibits anticholinergic and antihistaminic actions and controls rigidity and tremors in parkinsonism. (c) *Dose:* 1-2 mg t.d.s. Most satisfactory results, when combined with dextedrine. (d) Side effects: skin rash, xerostomia.

Artane (Benzhexol hydrochloride): (a) An atropine substitute which resembles atropine in action, but is less potent. (b) Controls both rigidity and tremors. *Dose:* 1 mg—1st day, 2 mg—2nd day, gradually increased till 6-10 mg/day is reached. (c) Side effects—xerostomia, blurring of vision, dizziness, nausea and nervousness.

Pagitane: (a) Chemically, related to artane, it is a white, crystalline solid and sparingly soluble in water. (b) It is more potent than artane and elicits less xerostomia, (c) It is more effective in controlling rigidity, akinesia and oculogyric crisis than in the reduction of tremors. *Dose:* 2.5 mg/day gradually increased to 5-75 mg/day. It is specially indicated in cases where artane fails.

Ethopropazine HCl (Parsidol): (a) A phenothiazine derivative which elicits antihistaminic, ganglion blocking, adrenergic blocking, CNS depressant and local anaesthetic activity. (b) It is most effective in controlling tremors. *Dose*—20-50 mg q.d.s., increased by 50 mg daily, till a total dose of 500 mg/day is reached.

Orphenadrine HCl (Disipal): It elicits anticholinergic, antihistaminic and antitremor activity. *Dose:* 50 mg t.d.s.

Caramiphen HCl (Parpanit): A synthetic antispasmodic drug, related to trasantin. *Dose:* 12.5 mg t.d.s. gradually increased to 200-600 mg/day.

Procyldine HCl (Kemadrine): Used in doses of 15-20 mg/day, in divided doses.

In addition to these drugs, *centrally acting skeletal muscle relaxants*—mephenesin, robaxin & soma are also sometimes used in parkinsonism.

THERAPEUTIC CONSIDERATIONS

Besides the numerous other uses of atropine, atropine derivatives and substitutes, their principal uses can be detailed under the following 4 conditions:

Mydriatic Use : (a) For routine ophthalmoscopy, where no cycloplegia is required, homatropine is the drug of choice. Sometimes neosynephrine, a sympathomimetic mydriatic, is also used. (b) For refraction in children, where a high degree of cycloplegia is desired, atropine is the drug of choice, while in *young adult* where only moderate cycloplegia is required, homatropine is used. (c) Atropine is also used in postoperative cases, as well as in *iridocyclitis*, for preventing adhesion formation.

Antispasmodic Use : In colic pains of the gastro-intestinal, biliary and urinary tracts, atropine, trasentin, novatropine and pavatrine are frequently used. They may be supplemented by morphine or pethidine, when the pain is very severe, needing besides antispasmodic, also central analgesic effect.

Antisecretory Use : This particularly refers to peptic ulcer in which, there is increased secretion of hydrochloric acid accompanied by pylorospasm. The drugs considered for this condition are: atropine, probanthine, pital and antrenyl. Their real efficacy in reducing gastric acidity in therapeutic doses is far from established but the antispasmodic action may be of some value in relieving the pain. Further, when combined with antacids they delay the transit and permit longer interaction between the acid and the antacid.

Antiparkinsonian Use : Drug therapy of parkinson's disease in *only symptomatic* trying to relieve the predominant symptoms. In view of the long therapy required, the hazard of tolerance formation with practically all the drugs has to be borne in mind.

It is customary to start the treatment with:

- (a) Artane, the basic drug for all symptoms.
- (b) For severe rigidity, spasm and muscle cramps, one may change to benztropine sulphate.
- (c) For severe uncontrolled tremors, parsidol or hyoscine should be tried.
- (d) Hypersensitive elderly patients are best treated with a combination of thephorin and small doses of strammonium.
- (e) To control associated akinesia, lethargy and insomnia, dextrodrine and chlorpromazine may be used along with any of the above drugs.

In general, postencephalitic parkinsonism responds best to drug treatment, idiopathic type moderately well and arteriosclerotic type, hardly to any kind of medication.

CHAPTER

11

SYMPATHOMIMETIC DRUGS

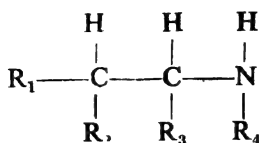
NATURAL AND SYNTHETIC AGENTS. THEIR STRUCTURE-ACTION RELATIONSHIP, PHARMACOLOGICAL ACTIONS AND THERAPEUTIC STATUS

[A group of natural and synthetic amines, which mimic the effects of stimulation of sympathetic nerve endings by acting on the adrenergic effector cells. The *dihydroxybenzene* derivatives — adrenaline, noradrenaline, isoprenaline and dopamine, possess shorter duration of action, the *monohydroxybenzene* group—neo synephrine and pargyline, intermediate action, while the *benzene* derivatives—ephedrine, amphetamine, tyramine—longer action, central stimulation and also stability of solution. Other compounds in this series are—pramex, vasoxyl and clopane, reputed for their vasoconstrictor action. The sympathomimetic drugs possess the typical adrenergic effect of: (a) passive mydriasis, (b) cardiovascular stimulation with predominant pressor response, (c) remarkable bronchodilatation, and (d) other plain muscle antispasmodic action.

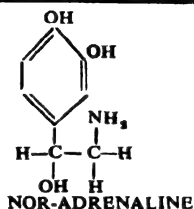
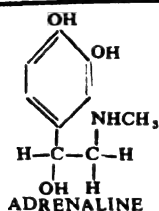
Unlike parasympathomimetic agents, these drugs have wider pharmacological actions and uses in (a) cardio-vascular failures—adrenaline, noradrenaline, methedrine and neosynephrine, are life saving drugs, (b) In bronchial asthma—adrenaline, ephedrine, and isoprenaline, along with cortisone and antihistaminics, are invaluable. Cortisone and aminophylline are particularly indicated in status asthmaticus, while isoprenaline, because of its actions on beta-receptors, in hypertensive asthmatics, (c) in other allergic disorders—adrenaline and ephedrine and not noradrenaline, are indicated, (d) as nasal decongestant— clopane, pramex and benzedrine, as inhaler or as drops, (e) as C. N.S. stimulant, dexedrine, ephedrine and in (f) peripheral vascular disease, noradrenaline and nylidrine are considered.]

This is a group of drugs, comprising of natural alkaloids and synthetic amines, which mimic the effect of sympathetic nerve stimulation by acting on the receptors, supplied by postganglionic sympathetic nerve endings. The dihydroxybenzene derivatives are also known as *catecholamines*.

Classification: Based on the basic chemical ring attached at R_1 position:

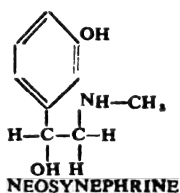
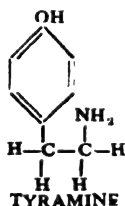


DIHYDROXY-BENZENE DERIVATIVES



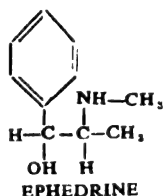
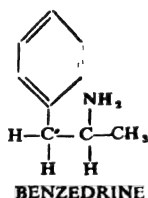
Adrenaline,
noradrenaline,
isoprenaline,
dopamine

MONOHYDROXY-BENZENE DERIVATIVES



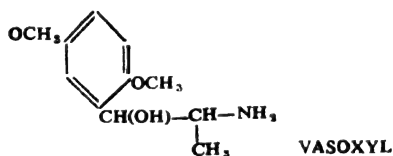
Synephrine,
neosynephrine,
paredrine,
tyramine

BENZENE DERIVATIVES



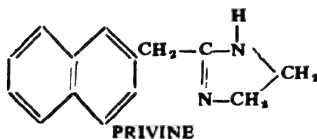
Ephedrine,
amphetamine,
methamphetamine,
wyamine

METHOXY-PHENYL DERIVATIVES



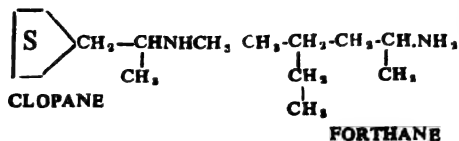
Vasoxy

IMIDAZOLE DERIVATIVE



Privine

MISCELLANEOUS



Clopane,
forthane

(a) For eliciting sympathomimetic action, the aromatic nucleus and side chain are important, the aromatic nucleus being separated from amino-nitrogen by a varying number of carbon atoms.

(b) Two OH groups in the benzene ring impart optimal sympathomimetic activity, but the central actions and duration of action are greatly reduced.

(c) Pressor potency is maximum when the two carbon atoms separate the ring from the amino group, while lengthening of the side chain abolishes the pressor activity.

(d) $-\text{CH}_3$ compounds are orally active, less readily destroyed, have a longer duration of action and also stimulate the C.N.S.

Dopamine, noradrenaline and adrenaline, the naturally occurring amines, are biosynthesised in the body, while ephedrine is of plant origin and the rest obtained synthetically.

These drugs produce their effect by acting on alpha, beta and mixed types of receptors. The chemical configuration of the adrenergic agent determines, which receptor will be activated and to what degree. The response to a particular agent—excitatory, inhibitory or mixed, will depend on this. Noradrenaline is the most potent activator of alpha receptors for excitatory response, isoprenaline of beta or inhibitory receptors and cardiac responses, while adrenaline activates both these receptors, producing a mixed response.

ADRENALINE

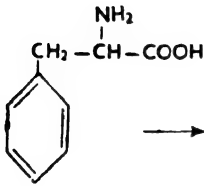
Also known as *Epinephrine*—is the suprarenal medullary hormone. It is a potent therapeutic agent with a wide range of clinical uses.

Historical: (a) The crude extract was studied by Oliver and Schaffer in 1895. (b) Pure adrenaline was isolated by Takamine in 1901. (c) Synthesis was effected by Stolz in 1904. (d) Structure—action relationship was determined by Berger and Dale in 1910.

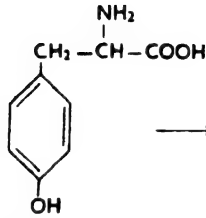
Preparation: (a) Natural adrenaline is obtained from freshly minced adrenals, macerated with dilute acid, the aqueous extract evaporated in vacuo and alcoholic extract purified by precipitation with ammonia. (b) Synthetic adrenaline is prepared by the interaction of—catechol + chloracetyl chloride = chloracetyl catechol. Treatment with methylamine and reduction, yields recaemic adrenaline, from which levo adrenaline is separated out by fractional crystallisation. It is 12-15 times more active than d-adrenaline.

Plate XII(a)

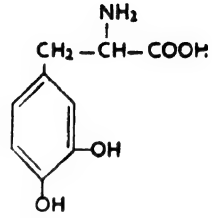
CHEMICAL NATURE OF SYMPATHOMIMETIC DRUGS



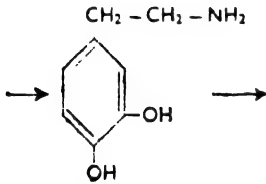
PHENYLALANINE



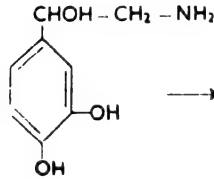
TYROSINE



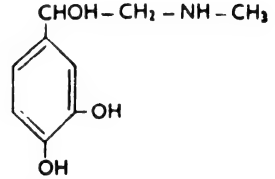
DOPA



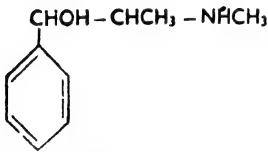
DOPAMINE



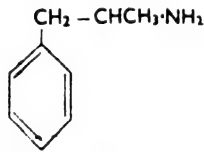
NOREPINEPHRINE



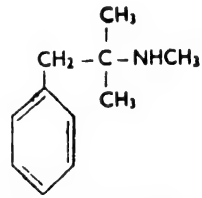
EPINEPHRINE



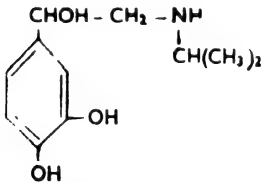
EPHEDRINE



AMPHETAMINE



MEPHENTERMINE



ISOPROTERENOL

Solution: Pale buff coloured crystals, sparingly soluble; forming salts with HCl and tartaric acids. The solution is easily oxidised and has to be stabilised and preserved by sodium metabisulphite, tricesol, or chlorbutol, at an optimal pH of 3-4. If the solution is pink or there is precipitation, it is to be discarded.

Doses: Adrenaline base—0.1-0.5 mg. Liq. Adrenaline HCl—1: 1000; 0.2-0.5 ml. Aqueous or oily solution for inhalation—1: 100.

Bioassay: Being a potent life saving drug, its potency is to be assayed—on B.P. of spinal cats (Elliot's method) against standard adrenaline powder of 50 to 52° rotation. The solution is also to be tested for sterility.

Administration: (i) *Oral:* Ineffective, due to destruction by digestive juices, local vaso-constriction and inactivation in liver and intestinal wall.

(ii) *Parenteral:* Ordinarily, the S.C. is the route of choice.

Intracardiac—in emergency heart failure cases.

(iii) *Inhalation and topical use* for local vasoconstrictive action only.

Metabolism: Rate of absorption is very slow due to vasoconstriction. It is inactivated in the body by several mechanisms: (a) *Oxidative-deamination*—by monoamine oxidase to form aldehydes and ammonia. (b) *Oxidation of phenolic hydroxyl groups* by cytochrome oxidase, forming o-quinone derivative, which cyclizes to form adrenochrome—a red coloured indole pigment. By polymerization, this is converted to brownish melanin-pigments. (c) *O-methylation*—by catechol-o-methyl transferase, an enzyme of major importance in the inactivation of circulating catechol amines—epinephrine and norepinephrine. It converts these amines to metanephrine and nor-metanephrine, which are then oxidised to 3-methoxy-4 hydroxymandelic acid. (d) *Conjugation*—with sulphuric or glucuronic acid to form sulphate or glucuronide, occurring in liver and intestine.

The products of enzymatic reactions, conjugated or unconjugated, along with trace amounts of free amines, are then excreted in the urine.

Actions: The typical actions are shown in Plate XIII, Figs. 35-38 and are detailed below:

C. V. System: Blood vessels—constriction of vessels going to skin, mucous membrane and splanchnic area. Dilates coronary vessels and vessels going to skeletal muscle. Cerebral blood flow is increased due to passive vasodilatation.

Plate XIII

SYMPATHOMIMETIC ACTIONS OF ADRENALINE

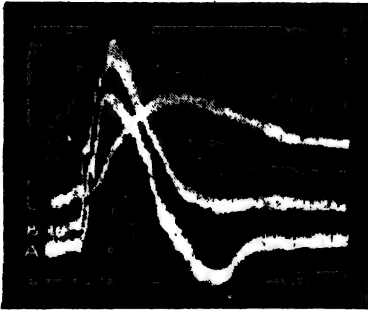


FIG. 35. *Dog blood pressure*: showing the effects of adrenaline (A), noradrenaline (B) and ephedrine (C). Noradrenaline causes a greater rise in blood pressure without causing any after fall, as adrenaline does. Note the slow but sustained pressor action of ephedrine.

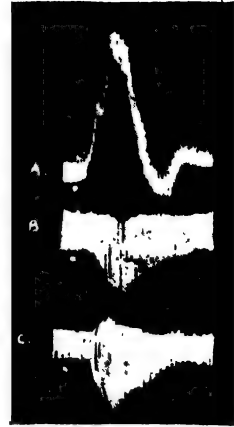


FIG. 36. *Dog blood pressure and auriculoventriculogram*: Note the stimulant action of adrenaline on the blood pressure and myocardium.

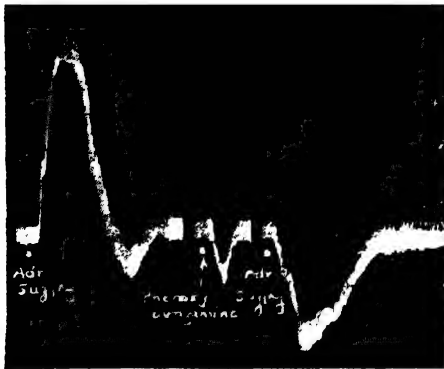


FIG. 37. *Vasomotor reversal of Dale*: Adrenaline causes an initial rise in blood pressure due to stimulation of alpha receptors and a subsequent after fall due to its action on the vascular beta receptors. After blockade of alpha receptors by phenoxybenzamine, the pressor response of adrenaline is converted into a depressor response,

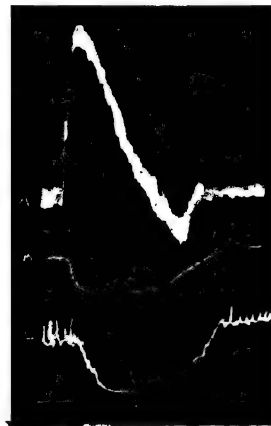


FIG. 38. *Record of B.P., splenic volume and intestinal motility*: showing the effect of adrenaline on blood pressure (A), splenic volume B and intestinal motility (C). Note the rise in blood pressure due to cardiac and vascular smooth muscle stimulation followed by vasodilatation resulting in after fall. The spleen contracts but intestine relaxes.

Heart: Three distinct effects: (a) Cardioacceleration through S.A. node (+ive chronotropic effect). At the peak of B.P. rise, slight reflex bradycardia. (b) Increase in force of contraction (+ive inotropic effect). (c) High doses alter rhythmic function of ventricles due to increased myocardial irritability causing extra-systoles, tachycardia and potential fibrillation. (d) Cardiac output is increased.

B.P.: Rise followed by a fall. (a) Because of increased cardiac output, the systolic pressure rises but due to lowering of peripheral resistance, diastolic pressure may fall. (b) Rise in B.P. is less with adrenaline compared to nor-adrenaline because of simultaneous action on β -receptors, which causes vasodilatation. If alpha receptors are blocked with ergotamine, then adrenaline causes a fall of B.P. instead of a rise because of predominant action on β -receptors. This is '*Vasomotor Reversal of Dale*'. (c) After cocaine the action of adrenaline is potentiated due to: (i) Vaso-constrictor effects—resulting in additive action. (ii) Inhibition of inactivating enzymes, (iii) Increased permeability of receptors, (iv) Physiological denervation effect.

Respiratory system: Initial apnoea, because of vagal stimulation, caused by rise in B.P. This is followed by deep respiration because of marked relaxation of bronchial muscles. Adrenaline is a powerful bronchodilator—but the action is transient.

Other actions: Relaxation of G.I.T. and detrusor muscles but constriction of sphincters. **Metabolism:** Increased glycogenolysis with increased blood-sugar level. **Eye:** Active mydriasis without cycloplegia mostly from intra arterial injection. The nictitating membrane is contracted. Contraction also of orbital muscles, producing exophthalmos. **Uterus:** Pregnant uteri contracted. Non-pregnant uteri relaxed, excepting in rabbits. **C. N. S.:** Excitement and restlessness when given I.V.; drowsiness and stupor when given intra cerebro-ventricularly.

Toxicity: depending on the dose—palpitation, throbbing headache and cardiac irregularities.

Uses: (a) Sudden cardiac arrest. (b) Acute bronchial asthma. (c) Other allergic conditions like hayfever, angio-neurotic oedema and acute anaphylactic shock, due to drug reactions. (d) Nitritoid crisis and hypoglycaemic shock. (e) Locally, as haemostatic.

Contra Indications: cardiac failure, fibrillation and peripheral vascular failure.

· NORADRENALINE

Also known as "*Arterenol*", was detected by von-Euler from adrenal medulla and sympathetic nerve endings (1946).

Chemically, it is adrenaline but without the methyl group on the N. Besides functioning as a neuro hormone, it also acts as a precursor for adrenaline.

Preparation: Inj-Levo-arterenol bitartrate, containing 0.2% of the salt. Ampoules of 4 c.c., 4 c.c. added to one litre of isotonic saline and given by I.V. drip; 0.5 to 1.0 ml./mt.

Actions: Essentially similar to *those of adrenaline* with the following differences: (a) Pressor effect—1.7 times greater, constriction of all blood vessels excepting coronaries. Both systolic and diastolic pressure increased. No secondary depression. (b) No acceleration but even bradycardia. No V.M. reversal. (c) Compared to adrenaline, < relaxation of rat uterus but > effect on rat colon. (d) Negligible antihistaminic and metabolic effects. (e) Adrenaline is produced by emotion, pain, trauma and hypoglycaemia, while noradrenaline is produced by circulatory stress, physical exertion and myocardial infarction. (f) Toxicity 1/8 of adrenaline.

Uses: An unchallenged life saving drug in *Peripheral vascular failure* and *anaphylactic shock*. It restores, B.P. without acceleration and strain on heart.

ISOPRENALINE

Isopropyl noradrenaline, has recently come into great prominence as a sympathomimetic amine.

Action: (a) It is a potent beta adrenergic agent with marked bronchodilator effect. (b) Like adrenaline, it produces cardioacceleration but a fall in B.P. which has increased its therapeutic value.

Preparation: Isoprenaline HCl—10-15 mg Tab./t.d.s./*sublingually* and 2% sol. for inhalation.

Uses: Drug of choice for *hypertensive asthmatics*—the sublingual administration prolongs the action. It is also useful in asthma resistant to adrenaline, chronic asthma, resistant to other therapies and *status asthmaticus*.

EPHEDRINE

An alkaloid, obtained from *Ephedra vulgaris* growing in China, India, Europe and America.

Preparation: Ephedrine HCl—15-60 mg. Tinct. Ephedra—2-4 ml.

The drug can be used orally in the form of tablets, or I.M. or local application as drops or spray—1-2% aqueous or oily solution.

It is absorbed from the G.I. tract as well as from the site of injection, demethylated in the body and 100% excretion in urine as norephedrine. It is an inhibitor of amine oxidase.

Actions: It is also an important sympathomimetic amine with slow but durable action.

C.N.S.: (a) Stimulation of cortex and medullary centres. (b) Neuromuscular transmission facilitated.

C.V.S.: Mild stimulation of heart. The B.P. rise is more from cardiac than peripheral vasoconstrictor effect.

Respiration: broncho dilatation from peripheral and central action, which, because of more prolonged nature and facilities for oral use, makes it a suitable adjunct and complementary to adrenaline therapy in asthma. **Plain muscle:** mydriasis, relaxation of detrusor muscle and constriction of sphincters. Compared to adrenaline, the special features are: (a) Stability of solution and oral administration. (b) Stimulation of C.N.S. and neuromuscular transmission. (c) Absence of V-M reversal and potentiation by cocaine and finally, (d) *Phenomenon of tachyphylaxis* from acute receptor competition. Due to incomplete demethylation, the receptors remain engaged and consequently, not ready for response to subsequent doses of ephedrine or adrenaline.

Toxicity: Headache, palpitation, insomnia, praecordial distress, dysuria and contact dermatitis.

Uses: (a) Bronchial asthma and allergic disorders. (b) Hypotensive states — used with spinal anaesthetics. (c) Narcolepsy, myasthenia gravis, combined with belladonna and (d) nocturnal enuresis.

BENZEDRINE

Also known as *amphetamine*, is a phenyl isopropyl amine derivative, resembling ephedrine but producing greater stimulation of cortex. The

pressor effect is only 1/100 of adrenaline. It is available in *d*-, *l*- and racemic forms, *d*-form, known as '*Dexedrine*', is two times more active on the C.N.S.

COMPARATIVE TABLE

	<i>Adrenaline</i>	<i>Noradrenaline</i>	<i>Ephedrine</i>
Chemistry	Catecholamine	Catecholamine	Benzene derivative
Source	Natural & synthetic	Natural	Natural
Route of administration	S. C.	I. V.	Oral or I. M.
Enzymatic destruction	Yes	Yes	No
Heart	Acceleration	Bradycardia	Acceleration
Pressor effect	Quick and short	More marked	Slow and prolonged
Vessels	Constriction	Constriction	Little effect
V. M. Reversal	Present	Absent	Absent
Bronchodilatation	Marked and prompt	Nil	Moderate and prolonged.
Hyperglycaemia	Present	Absent	Absent
Nictitating membrane	Contraction	Only after denervation	Absent
C. N. S. stimulation	Less	Less	Appreciable
Tachyphylaxis	Absent	Absent	Present
Antiallergic action	Present	Absent	Present

Preparation : Volatile liquid with burning taste. *Benzedrine sulphate* — Tabs. of 10 mg; *Benzedrine inhaler* 1%.

Actions : Stimulation of C.N.S. and in higher doses, headache, palpitation, agitation and insomnia, resembling other analeptics. Also C. V. stimulation of myocardial nature, bronchodilatation and phenomenon of tachyphylaxis. It is not used in asthma.

Mode of Action : An inhibitor of amine oxidase, the amines are spared and the action takes place by substrate competition.

Uses : (a) Allergic V.M. rhinitis and sinusitis. (b) Narcolepsy — 10-30 mg. (improvement in 100% cases and even when Ephedrine fails.) Also psychoneurosis, melancholia and myasthenia gravis. (c) Drug addiction and alcoholism — used as a stimulant.

Caution: Not to be abused before examination, as it may give drug habit like *caffeine* and *nicotine*.

OTHER DRUGS: **Methedrine:** Related to benzedrine but more potent with regard to C.N.S. and C.V. actions. Used to combat post-operative hypotension and C.N.S. depression in 15-30 mg/I.M. **Privine and Clopane:** Synthetic imidazole and propane derivatives respectively, with marked local decongestant action. Used in V-M. rhinitis and sinusitis. **Neosynephrine:** Chemically, intermediate between ephedrine and adrenaline, with an OH group in the benzene ring. It is less potent but with prolonged pressor effect, without cardiac or C.N.S. action, lasting for half an hour. It is used as nasal decongestant—0.25—1 % sol. and as mydriatic (2.5-10%), combined with butacaine, to avoid irritation. **Nylindrine:** A synthetic sympathomimetic amine, possessing only the vasodilator component. It increases the peripheral circulation and its action is mediated through the inhibitory pathways and not by adrenergic blockade. Used in *Peripheral vascular diseases* (6 mg. tab; 3-6 tab/day).

THERAPEUTIC CONSIDERATIONS

The sympathomimetic amines find their clinical uses on the basis of their three selective stimulant actions on— (a) Alpha receptors of peripheral blood vessels in *hypotensive states* — Nor-adrenaline, (b) Beta-receptors present in cardiac and smooth muscles. for *cardiac arrest* and *bronchial asthma* — Adrenaline and isoprenaline, and (c) C.N.S., in depressive conditions — Ephedrine, dexedrine.

Bronchial Asthma: An allergic disorder with paroxysmal bronchoconstriction, dyspnoea, wheezing and coughing. In severity, it may range from mild wheezing to status asthmaticus.

Sympathomimetic amines, other bronchial antispasmodics, antihistaminics and antitussive drugs are used for symptomatic relief, but the prospect of complete cure is remote.

Acute attack: *Liq. adrenaline HCl* 1:1000—0.5 ml. S.C. repeated after 30 mts. If necessary, isoprenaline sulphate—20 mg. tab. sublingually. Attack may be prevented by giving *ephedrine*—10-60 mg. t.d.s.

In hypertensive asthmatics— (i) *Aminophylline* 0.25-0.5 gm. in 10-20 ml. of H₂O or 500 ml. of 5% glucose solution I. V. drip. (ii) *Cholinetheophyllinate*—200 mg/Os. t.d.s. (iii) *Phenobarbitone* 30 mg. t.d.s.

Other drugs like antispasmodic, expectorants, antibiotics and *corticosteroids* are also to be considered for the management of bronchial asthma.

Status asthmaticus: 0.1 ml. of adrenaline (1:1000) S.C. every 1-2 mts till attack terminates. As much as 8 ml may be required. If unsuccessful, *aminophylline* or *prednisolone* and oxygen therapy may be tried.

COMPARATIVE USES

	<i>Vascular failure</i>	<i>Spinal anaesthesia</i>	<i>Local anaesthesia</i>	<i>C. N. S. stimulation</i>	<i>Asthma</i>	<i>Allergic disorder</i>	<i>Decongestant</i>	<i>Myasthenia gravis</i>	<i>Peripheral vascular disease</i>
Cardiac arrest									
Adrenaline	Nor-adren. Methedrine & Neosyneph.	Ephedrine Neosyneph. Noradrenaline	Adrenaline Neosyneph.	Dexedrine Ephedrine	Adrenaline Ephedrine Isoprenaline	Adrenaline Ephedrine	Clopane Privine Benzedrine	Ephedrine	Nylindrine

Chronic asthma: Ephedrine sulfate — 30-60 mg. t.d.s., Cholinetheophyllinate—200 mg./Os, b.d. or t.d.

Prolonged use may result in the development of '*epinephrine fastness*', which can be corrected by discontinuing the drug for some days and replacing it with *isoprenaline*. For the treatment of the respiratory infections tetracycline or ampicillin—250 mg./Os. q.d.s. for 5-7 days may be prescribed. Antihistaminic therapy may sometimes be considered.

Peripheral Circulatory Failure: Characterised by sudden fall in circulating blood volume, venous return and cardiac output, with generalised tissue anoxia. This may be the result of: (a) Loss of fluid and electrolytes — haemorrhage, trauma, burns, diarrhoea, vomiting, diabetes, Addison's disease. (b) Sudden shock without loss of blood or fluids from reflex vasodilatation, with pooling of blood in the periphery, associated with cardiac infarction, massive pulmonary embolism perforation of peptic ulcer, etc.

Management comprises of : (a) Treatment of cause, and correction of blood or fluid loss, by transfusion of blood substitutes — plasma, whole blood. (b) Management of peripheral stasis and resistance by viscosity reducing dextran, (c) Use of Sodium bicarbonate 7.5% (100-150 ml) I.V. as base buffer, (d) Control of infection by antibiotics and protection of kidney ischaemia by mannitol diuresis (20%, 100 ml or more) (e) Noradrenaline 4 mg. in 500 cc. of 5% glucose — I. V. drip-rate adjusted to maintain systolic B. P. at 100 mm. of Hg. For prolonged action—mephenteramine sulphate—30 mg I.M., methoxamine—15 mg I.M. (f) Vasodilators—phenoxybenzamine 1 mg/Kg or chlorpromazine or phentolamine—1-2 mg/Kg I.V. with blood substitutes; (g) I.V. steroid for protectin from shock. (h) Vasoxyl, 10 to 15 mg I.M. or 50 mg in 500 ml I.V. drip. It is as effective as noradrenaline and does not cause increased myocardial irritability, resultant arrhythmia and local necrosis.

CHAPTER

12

ADRENERGIC BLOCKING AGENTS

RECEPTOR BLOCKADES AND SYMPATHOLYTIC DRUGS- ERGOT ALKALOIDS AND SYNTHETIC COMPOUNDS

[The terms — *adrenergic blocking* and *sympatholytic action* are quite different. The former refers to the blocking of sympathetic activities from *circulating adrenaline* on the adrenergic receptors, while the latter, prevents the action of sympathetic stimulation and thus release or emptying of stores of catecholamines, for acting *locally*, on the receptors. These agents are therefore known as sympatholytic or *adrenergic neurone blocking agents*. The adrenergic blocking agents may block α receptors — ergot alkaloids, imidazole, dioxane and β -haloalkylamine derivatives — priscoiline, benodaine, dibenamine respectively and the sympatholytic agents are: bretylium, guanethidine, reserpine and α -methylDOPA. Adrenergic β -receptors are blocked by DCI and nethalide.

The effects of these blockades are complex and variable, affecting C. V. system and blood pressure, C.N.S., G.I.T. uterus and eye. As a general rule, blocking of α -receptors results in inhibition or reversal of *excitatory responses* and prevention of adrenaline induced cardiac arrhythmia without affecting the inhibitory ones; while, blocking of β -receptors, leads to the inhibition of inhibitory responses.

They all possess a number of *side-effects*, of which, postural hypotension, local tissue damage, CNS stimulation, G.I. upset, gangrene, tachycardia, arrhythmia and paraesthesia, are the common ones.

Their special uses comprise of: (a) migraine, (b) peripheral vascular diseases, (c) diagnosis of pheochromocytoma, (d) hypertension, and (e) thyrotoxicosis, but practically all with mixed results.]

Since the earlier work of Dale and Barger, Fourneau, Bovet, Nickerson and many others, different terminologies have been introduced in literature for this group of drugs, depressing sympathetic activities, which occur as a result of two factors: (a) Adrenaline secreted by adrenal medulla circulating in blood and causing wide-spread sympathetic activities. Drugs which prevent this action by blocking of receptors, are called "*Adrenergic blocking agents*", (b) Sympathetic nerve stimulation resulting in the release of catecholamines from their local stores which then act on the local adrenergic receptors. These drugs, which prevent effects of sympathetic stimulation by depressing

higher centres or by preventing the release or causing emptying of the stores or by reducing the synthesis of catecholamines, are the true "*Sympatholytic or adrenergic neurone blocking drugs*". This latter group of drugs will be studied in the chapter of "*hypotensive drugs*".

The blocking drugs may prevent the action of sympathetic mediators by restricting their entry or access into the effector cells or adrenergic receptors. They do not have any action of their own in this particular respect but they have other actions, which may partly modify their individual responses. They can act in the presence of mediators either by blocking, by apparent reversal or by selectively antagonising certain actions only.

CLASSIFICATION

	<i>Adrenergic Blocking Agents</i>	<i>Sympatholytic Agents</i>
Alpha receptors	Ergot alkaloids — Ergotamine, DHE45	Central — Chlorpromazine
	Imidazole — Prisoline, Regitine	Neuron blocker — Bretylium
	Dioxane — Benodaine	Catechol depletor
	Dibenzazepine — Ilidar	— Reserpine, — Guanethidine.
	β -haloalkylamine — Dibenamine, — Dibenzylamine	Synthesis reducer — α -methyl DOPA
	Misc. alkaloids — Yohimbine, Bulbocapnine	Xylocholine
Beta receptors	Dichlor isoproterenol (DCI) Nethalide	

Chemistry: (a) All are tertiary amines and their conversion to quaternary or secondary forms, abolishes adrenergic activity. (b) Benzodioxanes do not act as such, but are converted to an active intermediate product. (c) β -haloalkylamine structure only prolongs the action but is not essential for the activity. (d) All these compounds are structurally dissimilar to adrenaline and hence *may not* act by *competitive blockade*.

Common Properties: *C. V. system:* In small doses all the members, excepting ergot, cause a fall of standing B.P., while in large doses, also of supine B.P. The latter produces a rise in B.P. due to direct vaso-

constriction. *Pressor response to adrenaline* is prevented in small doses, reversed in larger doses (reduced or absent in pithed cats) and in very large doses, in exceptional cases, abolition of reversal sometimes. *Pressor responses, obtained reflexly* by carotid compression or stimulation of the central end of vagus, is abolished, due to the sparing of β -receptors, on which circulating adrenaline is able to act powerfully now. There is dilatation of the vessels with fall in B.P.

On the *coronary flow*, *ergotamine* shows direct constrictor action. *Dibenamine* and *benodaine*, do not block epinephrine induced dilatation. *Tolazoline* (priscol) potentiates epinephrine induced dilatation and *ilidar* blocks epinephrine induced dilatation. *Cerebral flow* is not controlled by adrenaline and, therefore, response to blocking agents is inconsistent. Ergot, however, increases the flow, due to its stimulating action on B.P.

Heart: Chronotropic response in frog heart is blocked by dibenamine and ergot. *Inotropic response* is not affected by any (except D.C.I.). Cardiac arrhythmias due to anaesthetics are prevented by the blocking agents. This is not due to the action of these drugs on the heart, but because of their action on peripheral resistance, which is lowered, thus reducing the load on the heart.

C. N. S.: In small doses stimulation, (weak clonic convulsions) and in large doses,—depression (asthenia, ataxia, stupor). This is applicable particularly to ergot.

G. I. T.: Adrenaline induced relaxation is not blocked completely. Ergot has direct stimulant action on *G. I. T.* *Hyperglycaemia*, due to adrenaline, is not prevented.

Miosis: is produced by all, except ergot, which causes an initial mydriasis due to direct action on radial fibres.

Uterus: Usually no action except in the case of *ergot*, which causes direct myometrial stimulation. Adrenaline induced contraction is blocked, but adrenaline induced relaxation, is not, as it is mediated by β -receptors.

Side-effects: (a) Postural hypotension is common to all. (b) Local tissue damage and C.N.S. stimulation by dibenamine and dibenzylene. (c) Nausea, vomiting and gangrene of extremities, by all (d) Tachycardia, arrhythmia, anginal pains, diarrhoea, flaring up of peptic ulcer, pin and needle sensations by priscoline, regitine and benodaine, more particularly.

Uses: Besides a long list of general and occasional uses of these drugs in hypertension, painful neurovascular conditions; herpes zoster

etc., the *special uses* are: (a) Migraine, (b) Peripheral vascular diseases. (c) Diagnosis of pheochromocytoma.

Ergotamine and D.H.E.₄₅ are also used in *thyroid storm* to reduce the sympathetic overactivity. Similarly, *Priscoline* I. V. is used in ventricular failure.

ERGOT ALKALOIDS

Lysergic acid derivative, obtained from rye, infested by the fungus, *Claviceps purpurea*, converting its ovary to a series of aminoacids. (Plate X, Fig. 30).

Of the three important alkaloids, only ergotamine and its hydrogenated derivative — D.H.E.₄₅ require to be considered as adrenergic blocking agents here, while, ergonovine and ergotoxine will be studied in the chapter of *oxytocic drugs*.

Ergotamine Tartrate: Very little soluble; *Tablets*: 1 mg. and *Ampoules*: 1 mg/2 cc. It is slowly absorbed from the G.I.T. The oral dose is 4 times the I.M. dose.

Actions: Besides general adrenergic blocking effect, the essential actions are: (a) Plain muscles stimulation — uterus, intestine, blood vessels, (gangrene in toxic doses). (b) Hypotension and prevention of adrenaline induced cardiac arrhythmias from sympatholytic action. Inotropic and chronotropic actions are not blocked but hyperglycaemic response is. (c) Various degrees of C.N.S. action — stimulation of vagal and vomiting but depression of respiratory and V.M. centres and also of carotid sinus pressor reflex. (d) Initial mydriasis due to direct stimulation of radial muscles, followed by miosis from sympatholytic effect.

Combination with caffeine, as in *cafergot*, potentiates ergotamine effect in migraine.

D.H.E.₄₅ (Dihydroergotamine), derived from ergotamine, is a good blocking agent and is devoid of direct vasoconstricting action. It is also much less toxic. **Dose:** 1 mg. I.M. to be repeated after 1-2 hrs. It is equally potent, and has less side effects. It is given only by injection.

Uses: (a) As sympatholytic agent, (b) Hypertension, (c) Peripheral vascular diseases, (d) Thyrotoxicosis, (e) Eclampsia, (f) Migraine.

IMIDAZOLINE DERIVATIVES

Priscoline or Tolazoline: A benzyl imidazoline, which besides producing adrenergic blockade lasting for 2-3 hours, possesses several impor-

tant actions, resembling *acetylcholine* in G.I.T. stimulation, adrenaline tachycardia, *histamine* in direct vasodilatation and curare in skeletal muscle weakness. It causes coronary vasodilatation.

HCl salt: 25-75 mg/orally or I.V. 1-4 times/day.

Side-effects: formication, tachycardia, weakness.

Uses: (i) Choice drug for *Peripheral vascular* and *Arteriosclerotic vascular diseases*. (ii) Also used for preventing gangrene caused by I.V. infusion of noradrenaline.

Regitine or *phentolamine*: The methane-sulphonate and the HCl salt—50 mg. tab. 4-6 times a day, is used. It is more potent than prisolone and blocks pressor responses to adrenaline, as well as sympathetic nerve stimulation. *Uses*: (a) Diagnosis of pheochromocytoma—5 mg. I.V. or I.M., with no consequent rise in B.P. after adrenaline, (b) *Peripheral vascular diseases*.

Side-effects: Tachycardia, hypotension, nasal stuffiness, G.I. distress.

DIOXANE DERIVATIVE

Benodaine HCl—10-20 mg. I.V.: (a) It does not act as such but is converted to an active metabolite and is the shortest acting drug in this series. (b) It blocks the inotropic action of adrenaline on the heart. (c) Due to continued side effects, its use for the diagnosis of pheochromocytoma has been replaced by Regitine.

DIBENZAZEPINE DERIVATIVE

Ilidar phosphate: A potent short acting adrenergic blocking drug, which paradoxically, blocks adrenaline induced coronary dilatation. It, however, does not block the inhibitory action of adrenaline on other smooth muscles. *Dose*—25 mg. tablet; b.d. or t.d.s.

β -HALO-ALKYL AMINES

Dibenamine: A nitrogen mustard derivative and an oily liquid base. The HCl salt is crystalline and soluble in water.

Actions: (a) *Specific adrenergic blocking action* as shown by: (i) V.M reversal, (ii) Inhibition of retraction of nictitating membrane by adrenaline and prevention of mydriasis, (iii) Blocking of cyclopropane cardiac arrhythmias, (iv) Unlike other agents, it blocks catecholamines, released by nerve stimulation, to some extent.

(b) C.N.S. stimulation — convulsion.

(c) Local tissue damage.

Uses: (a) Most promising adrenergic blocking drug but toxic, undependable and full of side effects. (b) Hypertension — 4-6 mg./kg. I.V. (c) Raynaud's disease. Action in 1-2 hours, lasting for several days, but may produce orthostatic hypotension.

MISCELLANEOUS

Yohimbine: An alkaloid of the African tree, *yohimbeche*. Its chemical structure resembles reserpine. Dose: 5 mg.

Action: It produces C.N.S. stimulation, followed by depression and also stimulation and erection of penis by vasodilatation. It is wrongly used as a popular aphrodisiac though it does not increase libido.

Use: A pharmacological tool with no therapeutic value.

Dichloroisoproterenol: (D.C.I.): A newly discovered derivative of Isoprenaline, which usually antagonises the beta component of the sympathomimetic activity.

Actions: (a) The hypotensive effect of Isoprenaline is blocked, the pressor response to adrenaline is increased and vasomotor reversal phenomenon abolished. The effect of noradrenaline remains unchanged. The positive inotropic and chronotropic effects, as well as, adrenaline induced cardiac arrhythmias, are prevented. (b) The bronchodilator, hyperglycaemic and uterine relaxant effects of adrenaline are also antagonised. (c) Although the relaxant action of isoprenaline on the intestine is inhibited, it does not very effectively block adrenaline induced relaxation. In high doses, it decreases the tone and amplitude of contraction of rabbit intestine.

Use: A pharmacologic tool for blocking beta-receptors.

CLINICAL CONSIDERATIONS

Migraine: A type of periodical hemicrania lasting for a day or two, preceded by prodromal symptoms, visual and other disturbances, and associated with nausea, vomiting and excruciating headache, often starting with the sunrise. The etiology is not fully known, as both vasodilatation and vasoconstriction of cerebral vessels, may produce the syndrome.

Treatment comprises of: (a) Heavy doses of analgesics: aspirin or saridon, for aborting an attack, with rest in bed in darkness. (b) Ergotamine tartrate or gynergin: 0.25 cc. I.M., repeated, if necessary,

with a total of 2 cc. in a day. *Orally*: 1 tab. every hour, 5 doses is less effective.

It works better in pulsating type of migraine and may palliate in 80-90% of the cases.

Other drugs in use are: *Cafergot* (caffeine+ergot) tablets and suppositories and *Wigraine* (ergotamine, caffeine bellafoline and phenacetin).

Peripheral Vascular Diseases: A condition, characterised by decrease in blood supply to the limbs due to: (a) Vasospasm: as in Raynaud's disease and frost-bite. (b) Organic obstruction of blood vessels, as in arteriosclerosis obliterans, Burger's disease, acute arterial occlusion. etc. There is ischaemic manifestation in the limbs, muscles, pain, ulceration and gangrene.

Drugs of choice: β -haloalkylamines, priscoline and ilidar are more useful in the former group. *Other Drugs in use* are nylidrin—duvalidan (Isoxuprine HCl, a derivative of hydroxy ephedrine with direct vasodilating effect. *Dose:* 10-20 mg. t.d.s. *Roniacol tartrate:* a nicotinic acid derivative, with slow and prolonged action and *cyclospasmol*, causing vasodilatation by direct musculotropic action.

Pheochromocytoma: A chromaffin tissue tumor of adrenal medulla, characterised by: (a) Increased secretion of catecholamines, (b) Paroxysmal attacks of hypertension.

Alpha adrenergic blocking drugs — *phentolamine* and *piperoxan* are used for its diagnosis. The former is also used in the preoperative and surgical management of these tumours. Their use is based on the fact that they block the effect of circulating epinephrine and produce an immediate fall in B.P., due to vasomotor reversal. *Phentolamine* or *regitine* is given in doses of 5 mg. I.M. or I.V. A positive response is indicated by a fall in B.P. of more than 20-30 mm. Hg. *Benodaine* HCl is used only in hospitalised patients, because of its alarming and potentially dangerous side-effects.

CHAPTER

13

GANGLION BLOCKING AGENTS

NATURAL AND SYNTHETIC COMPOUNDS. THEIR MECHANISM OF ACTION, THERAPEUTIC VALUE AND LIMITATIONS

[Sympathetic and parasympathetic activities are continuous, though mutually antagonistic. Suppression of one lifts the rider and enhances the activity of the other. The ganglion is important for both and there is no known drug which can selectively act upon one or the other in one direction only, of stimulation or depression. All these variables make actions complex and thus difficultly usable. Normally, ACh depolarises ganglion cells and facilitates nerve impulse transmission. The blockades occupy the receptors and act by (a) Persistent depolarisation — nicotine, (b) Competitive blockade — quaternary ammonium and methonium compounds, amines-mecamylamine, pempidine or (c) Inhibition of formation or release of ACh — procaine, hemicholinium and magnesium.

The blockade also produces peripheral vasodilatation, hypotension and impotence in the cases of the sympathetic and mydriasis, dryness of secretion and smooth muscle atony in the case of the para-sympathetic, thus considerably restricting their uses, to: (a) hypertensive crises, (b) peptic ulcer, and (c) bloodless surgery. This is also in very selected cases only.]

Sympathetic and Parasympathetic activities, though continuous, are mutually antagonistic to a certain extent and on the whole, beneficial to the subject. Reduction of parasympathetic activities gives rise to effects simulating sympathetic stimulation and reduction of sympathetic activities, results in the predominance of parasympathetic functions. Ganglia are important structures in both these systems, and drugs which block them, often produce complex actions, due to a number of variables involved.

Since there is no single drug which can act selectively on either parasympathetic or sympathetic ganglia, the pharmacological actions present a mixed picture. In certain organs, mainly the para-sympathetic activity is reduced, while in others, the sympathetic effects are involved.

Normally, acetylcholine, released at the pre-ganglionic nerve endings, activates and depolarises ganglion cells and facilitates transmission of nerve impulses. The ganglion blockades occupy the receptors and block ganglionic transmission through acetylcholine mechanism either

Plate XIV

ACTION OF GANGLION BLOCKING AGENTS

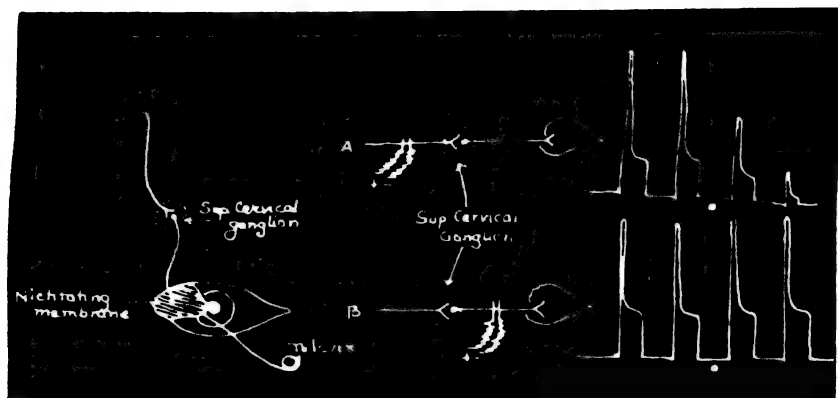


FIG. 39. *Schematic representation of the innervation of the cat nictitating membrane and record of its contractions :*

(A) Showing responses to stimulation of the preganglionic segment of the cervical sympathetic chain. Administration of hexamethonium at (•) results in reduction of the nictitating membrane contraction. However, stimulation of the postganglionic fibres results in restoration of the contractions showing that the site of action of the drug is at the superior cervical ganglion.

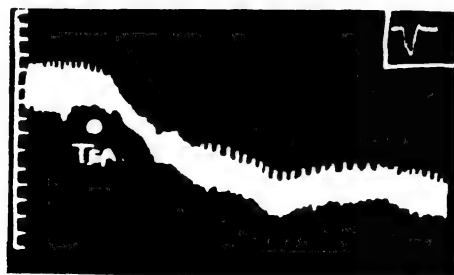


FIG. 40. *Dog blood pressure :* showing the gradual fall of blood pressure after tetraethyl ammonium (TEA) as compared to the transient fall after acetylcholine (inset).

by : (a) *persistent depolarisation* or (b) *competitive inhibition* or (c) *inhibition of formation or release of ACh*. In competitive inhibition, the blocking agents compete with ACh for the same receptors, because of structural similarity, though differing in activity.

CLASSIFICATION

Acting by Persistent Depolarisation	Natural Alkaloid Quaternary ammonium Compounds	Nicotine, lobeline Tetramethyl ammonium
Acting By Competitive Blockade	Quaternary ammonium compounds Amines	Tetraethyl ammonium, Penta & hexa methonium, Ansolyscn, Ecolid, Ostension, Presidal, Arfonad. Mecamylamine, pempidine
Acting By Inhibition of Formation & Release of Acetyl Choline		Procaine, hemicholinium, magnesium.

Mode of Study: (a) Inhibition of peristaltic reflex in isolated ileum of guinea-pig or rabbit, (b) Superior cervical ganglion — nictitating membrane preparation in cat, (c) Abolition of cardiac inhibition and fall in B.P. following peripheral vagal stimulation without affecting response to acetyl choline. (Plate XIV; Figs. 39 & 40.)

Patterns of Action

From sympathetic paralysis: (a) Fall of B.P. from removal of vasoconstrictor tone, degree depending upon the existing vasomotor tone. The higher the blood pressure, the greater is the fall. (b) The compensatory reflexes for maintaining constant B.P. during postural changes are abolished and there is sudden postural hypotension on standing. (c) Peripheral vasodilatation leading to the pooling of blood in extremities, rise of skin temperature and fall of peripheral resistance. This is accompanied by decreased blood supply to kidney. (d) Slowing of heart in some cases and also decrease of sexual function and impotence.

From parasympathetic paralysis: (a) Smooth muscles of viscera—relaxed, leading to constipation and difficulty in micturition. (b) Secretions decreased, resulting in dryness of mouth and reduced gastric acidity. (c) Passive mydriasis with cycloplegia from paralysis of ciliary muscle. (d) Heart rate may increase, if vagal tone is high.

In substance, the sympathetic blockades produce peripheral vasodilatation, hypotension and impotence, while parasympathetic blockades produce mydriasis, dryness of secretion and also smooth muscle atony, partially restricting their use in therapeutics.

NICOTINE

An old alkaloid, obtained from *Nicotiana tabacum*. A pyridine derivative, the base is a volatile liquid and the *sulphate* or *salicylate* salts are used.

Nicotine content in tobacco varies from sample to sample ($\frac{1}{2}$ —8%) and from preparation to preparation, the last 1" of the cigarette containing the maximum. It is partly burnt away and partly exhaled.

Action: (a) Brief stimulation, followed by paralysis of ganglia and myoneural junction; Stimulation followed by paralysis of C.N.S. Actions therefore irregular due to many variables. (b) Other important actions are bradycardia from vagal mechanism and tachycardia with tendency for hypertension due to sympathetic and V.M. stimulation and discharge of adrenaline. Also respiratory and G.I. irritation.

Toxicity: Acute and chronic: (a) Salivation, perspiration, emesis and exhaustion. (b) Electrocardiographic changes—extrasystole and inversion of T wave, (c) Tobacco amblyopia with retrobulbar neuritis.

Tobacco Habit: In different forms—smoking, chewing and snuff. Extremely widespread — U.S.A. alone manufacturing 3.7 billion cigarettes per year. A deep rooted addiction, persons dreaming of smoking long after giving up the habit.

Much work has been done in recent years about its ill effects on general health, longevity and carcinogenic property. The consensus of opinion seems to be that: (a) Light and moderate smoking, though may not be very injurious, is an expensive habit. (b) Heavy smoking may affect general health and longevity in the long run. (c) Potential carcinogenic agent for lungs, due to chronic irritation.

Contra Indication: Tobacco is interdicted in: (a) Angina pectoris and coronary thrombosis, (b) Hypertension and peripheral vascular disease, (c) Chronic respiratory troubles and peptic ulcer.

LOBELINE

An alkaloid of Indian tobacco, *Lobelia inflata*. The dosage forms are—Tincture, Fluid extract or *Lobeline sulphate* — 10 mg. S.C.

Action and Uses: (a) Resembles nicotine but greater stimulation of the medullary respiratory centre. (b) Used for resuscitating newly born babies in case of respiratory arrest.

QUATERNARY AMMONIUM COMPOUNDS

These drugs *ionise* in aqueous solution to form *negative bromide or chloride ions* and stable positive ammonium ions, which are responsible for the pharmacological responses.

Tetraethyl ammonium chloride (etamon chloride): It is poorly absorbed from G.I.T., but absorption is prompt after I.M. administration. It is rapidly excreted through the kidneys and appears in the urine unchanged. It is available in aqueous solution containing 100 mg/ml. *Dose:* I.V.—2-5 ml; I.M.—10-12 ml.

It blocks transmission of impulses through both parasympathetic and sympathetic ganglia, leading to vasodilatation, fall in B.P., decreased G.I.T. motility and secretion.

Uses: (a) Peripheral vascular diseases. (b) Coronary artery disease, and (c) Angina pectoris.

METHONIUM COMPOUNDS

Penta and Hexamethonium: (a) Chloride or bromide salts, are more potent and longer acting than T.E.A. (b) Their action is unpredictable by oral route and may cause G.I.T. irritation. Formation of *tolerance* is of common occurrence. (c) C_6 is available as solution of 25 or 100 mg/ml. *Initial Dose:* 50 mg S.C. or I.M./6 hrly. gradually increased, as tolerance develops.

Side-effects: Same as detailed earlier. May also produce *bromism* and *renal failure*.

Uses: (a) Malignant hypertension, (b) Peripheral vascular diseases, (c) Bloodless surgery, and (d) Peptic ulcer.

Ansolysen or Pentolinium Tartrate: (a) White crystalline stable powder, readily soluble in water and satisfactorily absorbed from the G.I.T. (b) It is available as Tab. of 40 and 100 mg and in solution containing 10 mg/ml. *Dose:* Oral — 60-600mg/day; S.C. or I.M. — 2.5 to 10 mg. (c) It blocks autonomic ganglia, and is 5 times more potent in blocking sympathetic ganglia and twice as potent as C_6 in blocking

parasympathetic ganglia, with much longer duration of action. It causes release of histamine and tolerance on prolonged use.

Side-effects: Same as C_8 .

Uses: Main use — treatment of *hypertension*.

Ecolid: (a) A long-acting potent autonomic ganglion blocking agent, 6 times as active as C_6 and twice as active as ansolysen. Tolerance is developed, but somewhat less readily. (b) *Dose:* Oral — Tab. 50 mg. Initially $\frac{1}{2}$ tab b.d., gradually increasing to 1—2 tabs b.d. S.C.— 5 mg/ml; Initial dose — 0.2 ml and gradually increased.

Ostensin: (a) A new drug, active orally, and with prolonged action and wider margin of safety, (b) It is available as 20 mg tab. Initial dose 40 mg/day, gradually increased till 120 to 140 mg/day. (c) Hypotension is evoked by ganglionic blockade, as well as, by depressant effect on the pressor areas in the brain.

Side-effects: Same as for other drugs but the incidence is less.

Arfonad: A short acting ganglion blocking agent, which produces hypotension partly through ganglionic blockade and partly by direct vasodilatation. Used mainly to induce controlled hypotension in surgical practice. *Dose:* initially — 10-30 mg I.V., followed by 20 mg. at 15 mts. intervals.

AMINES

Mecamylamine HCl (Inversine): (a) A secondary amine, which is rapidly and completely absorbed from the G.I.T. (b) Its action is slow and prolonged, lasting for 12 hrs. or more. (c) It potentiates the action of *d*-tubocurarine at the myoneural junction. It prolongs barbiturate sleeping time in mice. (d) It is mainly excreted through the urine and this is depressed in renal failure cases and when the urine is alkaline. (e) Tolerance is rare. (f) It is available as 2.5 mg. and 10 mg. tab. *Oral dose:* 2.5 to 60 mg/day.

Use: Mostly limited to *hypertension*.

Pemipidine: (a) A tertiary amine, completely absorbed from the G.I.T. and excreted rapidly. Its action starts in 2-3 hours and lasts for 6-8 hrs.

COMPARATIVE TABLE

Drug	Chemistry	Route of administr.	Potency	Duration of Action	Side effects	Special indications
Tetraethyl ammonium	N ⁺ ammonium comp.	I. V., I. M.	+	Short	Mydriasis Cycloplegia Constipation Urine retention Dry mouth.	—
Penta and hexamethonium	- do -	I. M.	++	Longer than T.E.A.	Also bromism and renal failure	Hypertension Peripheral vascular diseases
Ansolylen	do	OS/I M.	+++	Long	Same as T.E.A.	Hypertension
Ecolid	-- do	OS/S.C.	+++	Long	--do--	--do--
Ostensin	-- do --	OS	+++	Prolonged	--do--	--do--
Arfonad	--	I. V.	+++	Short	--do--	Bloodless Surgery
Mecamylamine	Secondary Amine	OS	++	Prolonged	--do--	Hypertension

(b) Bitartrate salt is used — *Orally* and HCl — *I.V.* (c) It is a weak neuromuscular blocking agent with wide safety margin and no tolerance even on prolonged use. *Dose:* 2.5 mg. t.d.s./os, increased by 2.5 mg till desired effect is produced — *I.V.* dose is — 5 mg.

Side-effects and Use: Same as for mecamlamine.

THERAPEUTIC USES

Hypertension: Ganglionic blocking agents were being used in the long term treatment of essential hypertension, but because of tolerance, erratic absorption and many side-effects, their use is reserved only for those cases, where an immediate fall in B.P. is necessary, as in 'malignant hypertension' and 'hypertensive crisis'. This will be detailed in the chapter of hypertension.

Bloodless Surgery: The use aims at inducing hypotension during surgical procedures to reduce bleeding and enhance visibility, in E.N.T. and Plastic Surgery, thyroidectomy, neurosurgery and cardiovascular operations. For this purpose, *arfonad* is usually given by *I.V.* infusion, 1:1000 solution, at an initial rate of 1-5 mg/min, the rate subsequently being varied according to the response of the patient.

Peptic Ulcer: Though these drugs are capable of reducing gastric secretion and motility, they have only limited application in this disorder as their effect is not selective and they produce side-effects, associated with parasympathetic and sympathetic ganlionic blockade.

CHAPTER

14

NEUROMUSCULAR BLOCKING AGENTS MUSCLE RELAXANTS

PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION, MECHANISM OF ACTION, CLASSIFICATION, TOXICITY, SPECIFIC ANTIDOTES AND USES

[The neuro-muscular junctions, which to an extent, simulate autonomic ganglia, comprise of two parts: (i) *End-plate* or the enlarged terminal ending of the motor nerve, and (ii) *Muscle sole-plate*—the contiguous muscles membrane. The transmission of impulse is mediated through ACh from motor terminals, the release of which, seems to be influenced by ions of Na and Ca. A nerve impulse, passing along a motor axon, produces the following changes: (a) nerve impulse, (b) depolarisation of NEP, (c) increase of ACh concentration, (d) depolarisation of MSP spreading to muscle cell, (e) contraction of muscle, (f) repolarisation of NEP, (g) fall of ACh concentration, (h) repolarisation of MSP, (i) relaxation of muscle. The cycle continues.

The muscle relaxants belong to two distinct categories:

A. *Peripherally acting* or acting through neuro-muscular junction.

B. *Centrally acting* or acting on the internuncial neurones in the spinal cord and midbrain. The *first group* may act by a number of mechanisms: (a) affecting release of ACh—procaine & magnesium; (b) competitive blockade—curare, flaxedil, metubine (c) depolarising agent—decamethonium and succinyl choline and (d) mixed block-mytolon, C₁₀. *Centrally acting*—mephensin, meprobamate, zoxazolamine, which latter, is an uricosaric drug but not used in gout.

The '*peripheral group*' finds important uses as (a) adjuvants to general anaesthesia, (b) orthopaedic manipulation, (c) endoscopic examination and (d) convulsion therapy and the '*central group*'—in (a) spastic skeletal muscle disorders — tetanus, strychnine poisoning, palsies, low back syndrome, etc.

The curariform drugs are liberators of histamine and are greatly toxic if any overdose is given. They find *specific antidotes in neostigmine and edrophonium or tensillon.*]

A group of drugs, old and new, natural and synthetic, which produces skeletal muscle relaxation and acts as adjuvant to general anaesthetics, by diverse mechanisms—(a) Blocking of neuromuscular junction and (b) Blocking of inter-neuronal transmission in the spinal cord.

Physiological Considerations: The neuromuscular junction consists

of two parts: the *end-plate* which is the enlarged terminal ending of the motor nerve and the contiguous membrane of the muscle—the *muscle sole plate*.

The transmission of activity from nerve to striated muscle is mediated by *acetylcholine*. The exact mechanism of release of ACh from motor nerve terminals is not known, except that sodium and calcium are necessary for this process and that it only occurs in response to a nerve impulse, which passing along a motor axon, produces following changes in successive steps: (a) A propagated wave of depolarization spreads over N.E.P., (b) As the N.E.P. depolarises, the concentration of ACh in the immediate vicinity of the nerve terminals instantly rises, (c) This leads to depolarisation of the M.S.P. and a propagated wave of depolarisation, spreads from the M.S.P. region over the muscle cells, (d) The muscle contracts, (e) N.E.P. becomes repolarised, (f) Concentration of ACh falls due to destruction by cholinesterase, (g) M.S.P. becomes repolarised and (h) Muscle relaxes.

ACh released, greatly increases the permeability of the end plate to several types of ions. This change in the end plate membrane is called depolarisation, since it involves the breakdown of the resting polarized state, in which, the outside of the membrane is positive and the inside negative. Depolarisation leads to generation of E.P.P., which, after reaching a threshold value, triggers off the much larger propagated action potential, associated with the contraction of the muscle fibre. The duration of E.P.P. is very brief, because of high ionic concentration at the M.S.P., which rapidly hydrolyses the liberated ACh and the end-plate rapidly returns to its resting polarised state, when, it is ready to respond to another nerve impulse. (Plate XV ; Fig. 41).

Peripheral Muscle Relaxants: The drugs which produce muscular relaxation by acting at the N.M.J., block transmission in three main ways—

1. *By competition:* These agents produce their action by competing with ACh for the end-plate receptors, to which, the latter normally gets attached. Their action, however, differs from ACh in that, their combination with end-plate receptors, is not followed by depolarization. They reduce the sensitivity of the end-plate to ACh and reduce the magnitude of the E.P.P., until it falls below the threshold, required to set off the propagated action potential. The size of the E.P.P. is reduced in proportion to the number of receptors occupied.

2. *By depolarisation:* These agents produce neuromuscular block by depolarisation of the end-plate. Their action resembles that of ACh

Plate XV

NEUROMUSCULAR TRANSMISSION

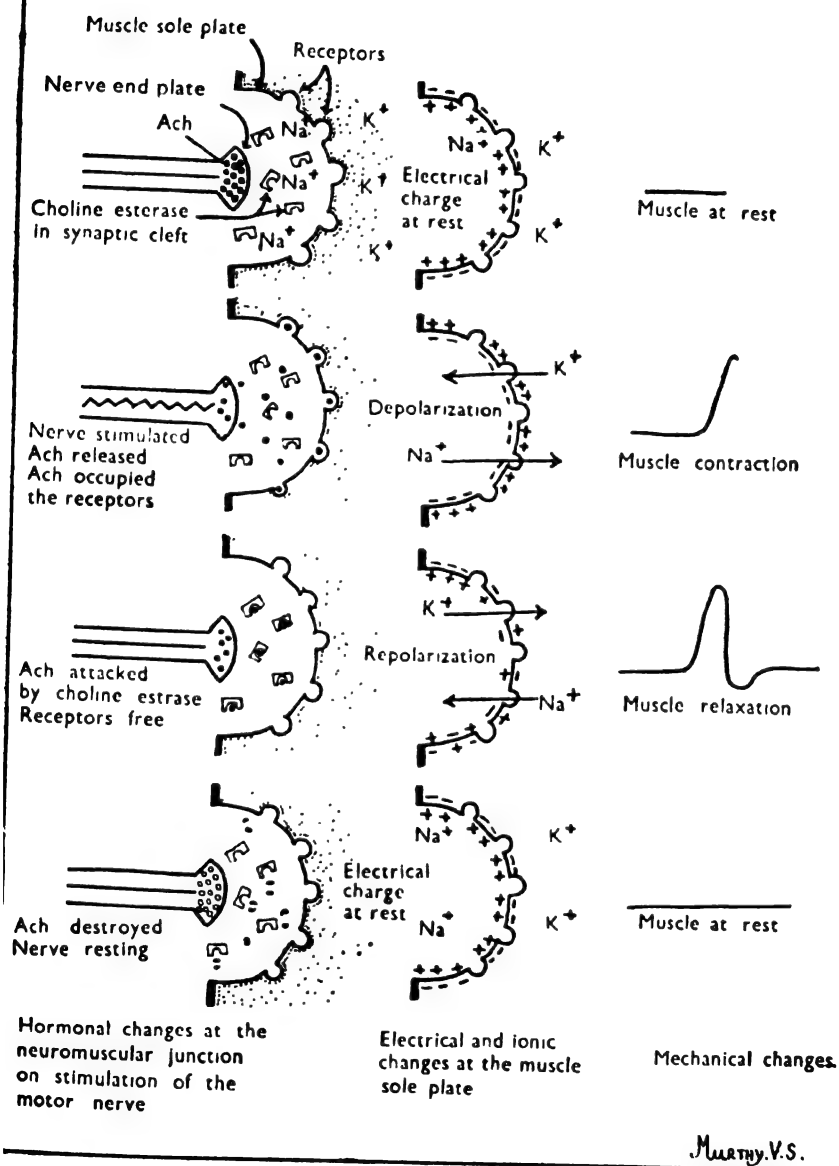


FIG. 41. Diagrammatic representation of the neuromuscular junction and transmission of impulses.

but lasts not for milliseconds but for minutes or even hours and spreads from the end-plate to the surrounding muscle membrane, rendering the latter inexcitable. They produce initial muscular twitches and increased contraction to indirect stimulation, before the onset of paralysis.

3. *Mixed block*: With some drugs, in certain animals, there may be mixed actions, in which, initial depolarisation is followed by a competitive type of block. This is known as *Mixed block* and exhibits some of the features of competitive block, some of the features of depolarisation block and some of which differ from both these mechanisms.

Central Muscle Relaxants: These agents produce flaccidity and muscular paralysis by acting centrally. They produce their action by acting on the *internuncial neurones*, at the level of the *spinal cord* and *midbrain*.

CLASSIFICATION

<i>Peripherally acting</i>	<i>Centrally acting</i>
I. <i>Affecting release of ACh</i> : Procaine, Botulinum toxin, Magnesium	<i>Propanediol derivatives</i> : Mephensin, Meprobamate, Methocarbamol, Sinaxar
II. <i>Competitive blockade</i> : d-tubercurarine, Flaxedil, Metubine, Laudexium	<i>Benzoxazole derivatives</i> : Zoxazolamine, Chlorzoxazone
III. <i>Depolarising agents</i> : Decamethonium, Succinyl choline	
IV. <i>Mixed block</i> : Mytolon, Decamethonium in some species, Tridecamethonium	

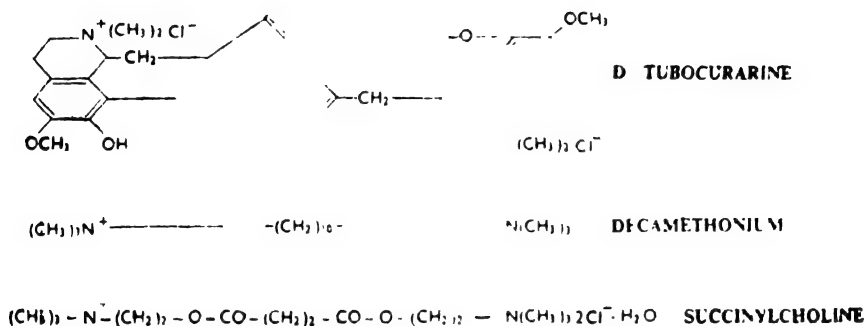
Note: Mytolon produces a competitive block in rabbit and dog, but a depolarising block in cat. Decamethonium, in monkey, rabbit, hare and dog, produces a block which has some feature of competitive block and others of depolarising block. Tridecamethonium acts on the tibialis anterior of cats, producing initial depolarisation, followed by a competitive block.

Mode of study : These drugs are studied as follows:

Peripherally acting: (a) Head drop method in rabbits, (b) Isolated phrenic nerve-diaphragm preparation of rat, (c) Gastrocnemius, Sciatic and Tibialis anterior preparations in cat or fowl and (d) Isolated Rectus abdominis of frog.

Centrally acting: Methods taking into consideration drug induced motor impairment, as index of activity in animals: (a) Ability to hang on a vertical or inclined screen, (b) Ability to grasp and hold weighted objects with fore-paws, (c) Ability to maintain position on a slowly rotating rod and (d) Antagonism of drug induced hypermotility by strychnine or metrazole.

Structure-activity relationship:



Illus. VI. S. A. R. of muscle relaxants

The structure action relationship of curariform drugs is complex. The peripherally acting agents are quaternary ammonium salts, the quaternisation of nitrogen having been responsible for muscle relaxation properties. The centrally acting group does not contain this type of nitrogen in them. In the former group, the distance of 14\AA between the quaternary nitrogen is of special significance for maximum curariform properties. Further in the depolarising agents, there must be 9 to 11 carbon atoms, while in the competitive group, this is not necessary.

PERIPHERAL BLOCKING AGENTS

As stated earlier, they encompass a large group of useful drugs acting by diverse mechanisms and largely exploited in therapeutics. The following deserve special reckoning.

CURARE

A collective term used to describe South American 'arrow poisons', obtained from the bark of a large number of poisonous plants—*Strychnos toxifera*, *Cocculus toxifera*, *Chondrodendron tomentosum* and popularly described as — 'calabesh curare', 'pot curare' and 'tube

curare'. The first two are no more available but the last one is prepared from the *Chondrodendron* species, with elaborate punctilious and ceremonial processes. These different types of curare contain different toxic alkaloids with varying pharmacological activities, *Calabash curare* being the most poisonous of all the three.

Tubocurarine, an impure alkaloid, was isolated from *Tube curare* by King in 1935 and from *Ch. tomentosum*, by Wintersteiner and Dutcher in 1943. The biologically standardised extract from *Ch. tomentosum*, called '*Intocostrin*', was used in 1939 in electroconvulsive therapy, spastic paralysis and introduced as an adjuvant to surgical anaesthesia by Griffith and Johnson in 1942.

Metabolism: (a) Limited absorption from G.I.T., the drug is therefore used parenterally. (b) Partly destroyed in liver and partly excreted in urine unchanged. (c) Enhanced toxicity in damaged conditions of kidneys.

Actions: (a) The classical experiment of Claude Bernard:

After ligation of one hind limb of frog, stopping circulation and then injecting curare into the lymph sac; *flaccid paralysis* on the unligated limb only was observed. This proves that curare acts peripherally and produces a competitive block without initial stimulation. Its action is potentiated by ether and patients with myasthenia gravis are hypersensitive to the drug. In higher doses, it blocks autonomic ganglia and vagus and stimulates spinal centres, which however, are masked by powerful peripheral paralyzing actions. The action of tubocurarine is reversible and antagonised by *neostigmine* and *edrophonium*.

Dose: 5-10 mg. I.V. after an initial test dose not exceeding 30 mg. in all. With ether only 30-50% of this dose is required. Duration of action—40 minutes.

Flaxedil: Also known as *gallamine triethiodide*, is a synthetic curariform agent, with $\frac{1}{5}$ the potency of curare. It was introduced by Bovet *et al* in 1946. It differs from tubocurarine in following respects: (a) It does not produce ganglionic block. (b) It causes tachycardia by an atropine like vagal block. (c) The N.M. blocking action is not enhanced by ether. (d) A weak histamine-liberator action is present.

It is used as adjuvant to ether and cyclopropane anaesthesia in a dose of 1 mg/kg. I.V. The duration of action is for 15-30 mts.

Metubine Iodide: A dimethyl ether of tubocurarine, it is 3 times more

potent than *d*-tubocurarine and depresses respiratory muscles to a lesser degree. One mg. of metubine = 3 mg. of tubocurarine. *Average initial dose* varies with the anaesthetic agent used; with ether it is 1.5 mg., nitrous oxide 4-5 mg., Cyclopropane 2-4 mg and Pentothal sodium 4-6 mg. I.V.

Mytolon Chloride: produces a mixed type of neuro-muscular block. It also inhibits cholinesterase and may produce signs of parasympathetic stimulation. In large doses, it blocks transmission through ganglia and is a weak histamine liberator. It produces less respiratory depression than other agents. *Dose:* 0.2 mg/kg. I.V. Duration of action—15-20 mts.

Laudexium Methyl Sulphate: A polymethylene bisisoaninolinium derivative, with effects similar to that of *d*-tubocurarine but the action is slow and prolonged. It is $\frac{1}{2}$ as potent as curare and the action is enhanced by ether. It does not release histamine or cause any ganglionic block. *Dose:* 0.2 to 1 mg./kg. I.V.

Decamethonium: It was introduced by Barlow, Ing., Paton and Zaimis group of workers in 1948 and has two quaternary nitrogen atoms, separated by a polymethylene chain, the blocking action being maximum when 10 methylene groups are present. The drug acts by depolarising the E.P.P. of muscle fibre and has a prompt onset and duration of action, as compared to tubocurarine. It produces less side-effects. Its action cannot be antagonised by prostigmine, tensilon, or any other drug and consequently, not much used in practice, in spite of 4 times greater potency than curare.

Succinylcholine Chloride: It is a suxamethonium compound, introduced by Bovet in 1949. It is a potent neuromuscular blocking agent, the block being caused by depolarisation, as in the case of decamethonium

- (a) The action is of very short duration — 5 mts. or less, after a single I.V. dose.
- (b) It is inactivated by cholinesterase and consequently, anticholinesterase drugs prolong its action.
- (c) It does not liberate histamine, but stimulates para-sympathetic and sympathetic ganglia and causes salivation and B.P. rise.
- (d) There is no antidote and edrophonium and neostigmine prolong its action.
- (e) The neuromuscular block is preceded by a brief stimulation with generalised twitchings.

(f) The drug may sometimes produce dangerously prolonged muscular relaxation, if its metabolising enzyme—an atypical pseudo-cholinesterase, is low in plasma, as a genetic factor.

COMPARATIVE TABLE

Drug	Mechanism of action	Potency	Duration of action	Ganglionic blockade	Histamine release
Tubocurarine	Competitive block	1	40 mts	yes	yes
Flaxedil	—do—	$\frac{1}{8}$	15-30 mts	—	weak
Metubine	—do—	3	—do—	—	—
Laudaxium	—do—	$\frac{1}{2}$	40-60 mts	—	—
Mytolon	Mixed block	1	15-20 mts	In large doses	weak
Decamethonium	Depolarising block	5	10-20 mts	—	weak
Suxamethonium	—do—	$\frac{1}{2}$	2-5 mts	—	yes

Action analysed : (a) Of all these agents, only *curare* is obtained from natural sources and the rest are all synthetic, (b) Effect of Tubocurarine and Laudaxium is potentiated by ether, (c) Initial twitchings are present with depolarising agents but they are more marked with succinyl choline.

Toxicity: The pattern of toxic manifestations in curariform drugs is practically the same for all the members, with slight variations in individual cases. These are: (a) Fatigue and muscular weakness, (b) Ascending paralysis of a flaccid nature, (c) Muscular twitchings more common with depolarising agents and convulsions, (d) Involvement of diaphragm, intercostal muscles, stoppage of respiration, the patient dying in plain consciousness.

Treatment: Artificial respiration, often with *heart-lung* machine, adequate oxygenation and specific antagonists, detailed hereafter.

TUBOCURARINE ANTAGONISTS

Two groups: (a) Anticholinesterase drugs and (b) Drugs having ACh like activities.

The first group permits accumulation of ACh and when sufficient concentrations have been attained, the action of the blocking agent

is overcome by simple competition. The drugs in the second group includes *neostigmine* and *tensilon* (edrophonium). It is now established that neostigmine possesses much structural similarity with ACh, both being quaternary ammonium salts and neostigmine possesses ACh like activity as shown in denervated preparations.

Edrophonium: Also known as *tensilon*, it antagonises the competitive group of N-M blocking curariform agents, its action starting immediately after I.V. Inj. and lasting for 10 minutes only. This is due to ACh, as well as anticholinesterase like actions. It can reverse atropine effect on heart and B.P. It has both muscarinic and nicotinic action, the latter being more prominent. In large doses, it induces N-M block by depolarisation. It does not antagonise dca and suxamethonium. Its action is shorter than that of neostigmine and it acts better when recovery from paralysis has already started. *Dose:* 10 mg/ml I.V.; to be repeated, if necessary.

In spite of potential toxicity of all the quaternary ammonium compounds like ganglion blockades, it seldom occurs, as they have a high safety margin of nearly 40.

INTERNEURONAL BLOCKING OR CENTRALLY ACTING AGENTS

These drugs depress polysynaptic or monosynaptic spinal reflexes either directly or through higher centres and act as muscle relaxants and anticonvulsants. They do not interfere with: (a) Nerve conduction, (b) N-M transmission, and (c) Muscle response to a direct stimulation.

PROPANEDIOL DERIVATIVES

Mephenesin or Myanesin: is a glycerol ether, in which $O:CH_2-CHOH-CH_2OH$ group, is essential for action. (a) It causes progressive skeletal muscular paralysis of a pattern, similar to *curare*, respiration being the last to be affected. (b) There is reduction of spasticity. The duration of action is short and this is a disadvantage. (c) The site of action is the spinal cord and only the polysynaptic, involving a large number of internuncial neurones and not monosynaptic reflexes, are abolished. It also acts on subthalamic and midbrain centres. (d) Mephenesin is effective in preventing '*strychnine convulsion*' but not '*metrazol seizures*'. It is also a local anaesthetic agent. (e) It is used for the treatment of various spastic conditions, including *tetanus* and *strychnine poisoning*. (f) It is also a muscle relaxant and is of use in anxious and tense

patients. (g) The untoward effects include lassitude, nausea, haemolysis and phlebothrombosis after I.V. Inj. *Dose:* Elixir—10% ; Tab—0.5 gm; 1-3 gm. t.d.s.

Mephenesin Carbamate: has similar properties but the action is more prolonged. Various combinations of mephenesin with barbiturates and salicylates are also available.

Meprobamate: Chemically akin to the above and combines muscle relaxant and tranquillising effect. The muscle relaxation is of longer duration than mephenesin, on oral administration. It does not depress monosynaptic reflexes. It effectively antagonises strychnine and metrazol convulsions. It is more used in maniac states and psychic disorders.

Frenderol: Glykotal and phonaglycohalan are some of the other compounds and used as anticonvulsants.

Methocarbamol: (a) It is as potent as mephenesin but long acting. (b) It has less hemolytic action and being more water soluble than mephenesin, is suitable for I. V. administration. (c) It is more active than mephenesin as antagonist of metrazol and maximal electro-shock seizures.

Carisoprodol (Soma): A derivative of meprobamate, which blocks polysynaptic reflexes. It does not block strychnine convulsions, but effectively antagonizes Metrazol seizures and also abolishes decerebrate rigidity.

Dose: *Tabs* of 350 mg. t.d.s. or *Caps* — 250 mg, *Side effects* — drowsiness, lassitude and weakness.

Styramate (Sinaxar): A longer acting muscle relaxant and anticonvulsant, available as *Tabs* of 200 mg. *Dose:* 200-400 mg t.d.s.

BENZOXAZOLE DERIVATIVES

Zoxazolamine: (a) It is a more potent and longer acting muscle relaxant than mephenesin, (b) It antagonises strychnine and metrazol convulsions and blocks polysynaptic reflexes, without affecting monosynaptic reflexes or myoneural function, (c) It also exhibits uricosuric action and has been tried in the treatment of *chronic gout*.

Side effects: drowsiness, nausea, vomiting, renal and hepatic damage. Due to toxicity, the drug has been withdrawn from the market.

Chlorzoxazone (Paraflex): A drug similar in action and potency to zoxazolamine, but without any uricosuric action. It is also very much less toxic. *Dose:* 250-500 mg. t.d.s. as tablets of 250 mg.

Therapeutic Uses: Though many, some are of established value, while others, are doubtful and undependable.

Peripherally acting group: Can profitably be used: (a) As *adjuvants* to *general anaesthetics* producing incomplete muscular relaxation

COMPARATIVE TABLE

	<i>Mephenesin</i>	<i>Meprobamate</i>	<i>Soma</i>	<i>zoxazolamine</i>	<i>Paraflex</i>
Polysynaptic Reflexes	Blocked	Blocked	Blocked	Blocked	Blocked
Monosynaptic Reflexes	Not „	Not „	Not „	Not „	Not „
Strychnine Convulsion	Antagonised	Less potent	No effect	Antagonised	Antagonised
Metrazol Seizures	„	Antagonised	Antagonised	„	„
Duration of action	Short	Long	Long	Long	Long
Uricosuric action	—	—	—	Present	—

as in the case of gases or in cases of abdominal and other operations, in which, perfect muscular relaxation, at a safe or reduced anaesthetic dose level, is desirable, e.g. cholecystectomy, internal podalic version etc. (b) *Orthopaedic manipulation* for dislocation, alignment of fractures. (c) Laryngoscopy, bronchoscopy and oesophagoscopy. (d) Prevention of trauma in *convulsive therapy*.

Centrally acting group is used for: (a) *Spastic musculo-skeletal disorders*: associated with palsies, paraplegia, chorea, tetanus, strychnine poisoning athetoid and dystonic states. Short duration of action and need for giving injection — are the limiting factors. (b) Relief of acute painful spasms in '*low back syndrome*' and myositis. (c) Lastly, for diagnosis of myasthenia gravis and detection of pain in nerve root compression, masked by spasms.

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SECTION

IV

LOCAL HORMONES, HISTAMINE AND ANTIHISTAMINICS

CHAPTER

15

LOCAL HORMONES

DEFINITION, NATURE AND ROLE

[The local hormones are tissue secretions which act locally regulating some of their physiological functions. Besides acetylcholine, adrenaline and noradrenaline, which also act as autonomic transmitters, dopamine, 5-HT and histamine belong to the established group of amine local hormones. Further, a number of polypeptides—angiotensin, bradykinin, substance P and some organic acids like darmstoff and GABA, are accepted like local hormones. Though their physiological roles are not definitely known *substance P* and *darmstoff*, found in the brain, intestine and dorsal nerve roots, are believed to be transmitters for the first sensory neurones and responsible for intestinal motility. *Bradykinin* is present in serum and is associated with vasodilatation and inflammatory reactions. Similarly, *kallikrin*, present in serum, is also a vasodilator but *angiotensin* is a vasoconstrictor. *5-HT*, present in blood, brain and intestine, is a non-cholinergic transmitter. *GABA* formed from glutamic acid in the brain, is a smooth muscle relaxant and probably an inhibitory transmitter in the CNS.]

These are chemical substances, formed within the tissues themselves and have a regulatory function on them. Although most of them have been demonstrated in the tissues, the exact physiological role of several of these members, is far from established.

CLASSIFICATION

AMINES	Acetylcholine, noradrenaline, adrenaline, dopamine, 5-hydroxytryptamine, histamine.
POLYPEPTIDES	Angiotonin, kallikrenin, bradykinin, kallidin, substance P.
LIPID SOLUBLE ORGANIC ACIDS	Darmstoff, GABA, SRS.

Acetylcholine, noradrenaline and adrenaline have already been discussed and histamine will be discussed in the following chapter. Acetylcholine and noradrenaline differ from other local hormones in that they also function as neurotransmitters at the neuroeffector and other synapses.

SUBSTANCE P

A potent, directly acting, smooth muscle stimulant, isolated by von Euler and Gaddum, from extracts of brain and intestine. It is also present, in large quantities, in the dorsal roots, posterior columns of the spinal cord and nuclei gracilis and cuneatus.

Actions. (a) It stimulates smooth muscles of the intestine and uterus. This effect is not blocked by ganglion blocking agents, atropine or antihistaminics. (b) After subcutaneous administration in mice, it causes inhibition of spontaneous activity and also sedation, while on I.V. injection in wild hares, it produces a long lasting taming effect. (c) Intracisternal or intraventricular injection in cats or rabbits causes stimulation of respiration and inhibition of spontaneous activity. (d) Reserpine, a tranquillising agent, has been found to produce an increase in the concentration of substance P in the rat brain.

Its suggested functions are: (a) Control of activity of intestinal smooth muscle (b) Chemical transmitter, released at the first sensory neurone, (c) Non-cholinergic transmitter in C.N.S.

BRADYKININ

It is present as bradykininogen in the α_2 -globulin fraction of the plasma and is released by trypsin or snake venoms. It directly stimulates intestinal smooth muscles, causes fall in B.P. in atropinised rabbits and is a potent bronchoconstrictor in guinea-pigs. It may play some role in functional vasodilatation, anaphylactic and peptone shocks and also in tissue reactions to inflammation.

ANGIOTONIN (HYPERTENSIN)

A vasoconstrictor polypeptide, formed by the action of renin on angiotensinogen and contained in the α_2 -globulin fraction of the plasma. It stimulates smooth muscles of intestine and uterus and produces vaso constriction of skin, renal and mesenteric vessels. It may be involved in the etiology of certain types of hypertension, caused by dysfunction of the kidney.

KALLIKRENINS

A high molecular weight, undialisable, thermolabile protein, obtained from its precursor—*kallikreninogens* and found in blood plasma, pancreas, salivary glands, saliva and kidney and probably produced by the action of trypsin and other proteolytic enzymes.

Action. (a) It causes a fall in B.P., increase in skin, muscle, brain and lung blood flow and a decrease in the splanchnic. It dilates coronary vessels, increases heart rate and antagonises pressor action of nor-adrenaline in the dog. (b) It stimulates dog and cat intestine, which are inhibited by adrenaline.

Use. (a) Peripheral vascular disease and (b) Hypertension, with mixed results.

KALLIDIN

A polypeptide present in serum., it causes hypotension and stimulates guinea pig intestine and uterus. Kallikrenin probably affects B.P. through the release of this substance.

VEM AND VDH (VASOEXCITOR AND VASODEPRESSOR MATERIALS)

VEM is formed by the renal cortex and VDH by the liver, spleen and skeletal muscles and is identical with ferritin, its iron containing protein. Both have opposite effects on precapillary sphincters and metarterioles. They sensitise these to the effects of local hormones, which increase or reduce the smooth muscle tone. They are probably involved in the homoeostatic mechanism, which regulates terminal vascular beds.

DARMSTOFF

Isolated by Vögt from the stomach and intestine of mammals., it directly stimulates isolated smooth muscle preparations and is probably involved in the regulation of motor activity of the G.I. Tract.

GAMA AMINOBUTYRIC ACID (GABA)

It was identified from mammalian brain by Roberts and Frankel and also by Amapara, Landua, Fuerat and Deales. It is distributed throughout the brain but the concentration in different areas, varies. It is higher in grey than white matter. It is formed by the decarboxyla-

tion of *l-glutamic acid* and is removed by transamination with *l-glutamic acid* and is removed by transamination with l-Ketoglutarate, yielding succinic semialdehyde. It inhibits the stretch receptor impulses in *cray fish* and this property has been utilised as a method of assay for GABA. It may either stimulate or relax isolated guinea pig ileum and reduce contractions induced by acetyl choline, histamine, 5-HT and nicotine. It is suggested that it may function as an inhibitory transmitter in the C.N.S.

5-HYDROXYTRYPTAMINE

Isolated as *Enteramine* by Erspamer from enterochromaffin cells of G.I. mucosa and as *Serotonin* by Rapport *et al* from Serum. It is widely distributed in animal and plant kingdoms and is present in intestine, blood platelets, brain, pine apples, bananas, stinging nettle and lowhages.

It is synthesised in the body from *tryptophan* as :



It is stored in the cytoplasmic granules in association with A.T.P.

5-HT is inactive orally, but is quickly absorbed when given parenterally. In the body, it is deaminated by MAO and is then excreted in urine as 5-hydroxyindole acetic acid.

Actions. These are extremely variable and differ not only between species, but also between animals of same species and even in successive tests.

Respiratory system: (a) Transient stimulation in dog and man with variable effects on rats, due to stimulation of carotid and aortico-chemoreceptors; while inhibition in cat, due to reflex vagal stimulation. (b) Broncho-constriction due to direct effect on bronchial smooth muscles.

C.V.S.: (a) Constriction of all the blood vessels except those of skeletal muscle, which are dilated. Increase in capillary permeability, only in rodents. (b) Positive inotropic and chronotropic effect on isolated heart and atria. (c) On I.V. injection, a brief depressor response, followed by a pressor phase and finally a more prolonged depressor phase. The first is due to stimulation of vagal endings in the coronary bed, the second to vasoconstriction, while the last phase is due to vasodilatation.

Smooth muscles: Increase in motility of the G.I.T. partly by acting

directly and partly by exciting intramural ganglion cells. It also stimulates smooth muscles of the uterus, urethra and nictitating membrane.

Sensory nerve endings: It stimulates a variety of sensory nerve endings, evoking intense pain when applied to the base of the blister. It sets up electrical activity in nerve fibres when given by close intraarterial injection.

Autonomic ganglia: It stimulates autonomic ganglia and facilitates ganglionic transmission.

C.N.S.: No effects are commonly observed as the drug cannot cross blood brain barrier. After intraventricular injections in cats, it causes—muscular weakness, swaying gait, tendency to adopt a sleeping posture and a catatonic state.

Physiological role: May play a role in the regulation of intestinal motility and as a non-cholinergic transmitter in certain areas of the C.N.S.

COMPARATIVE TABLE

<i>Local Hormone</i>	<i>Distribution</i>	<i>Smooth Muscle</i>	<i>Blood Vessels</i>	<i>Physiological Role</i>	<i>Use</i>
Substance P	Brain, Intestine, Dorsal roots	Stimulated	Dilatation	1st neuro-ne transmitter, Intestinal motility	Pharmacological tool
Bradykinin	Serum	—do—	—do—	Functional vasodilatation, Inflamm. reaction, Anaphyl. shock	
Kallikrein	Pancreas, Saliv. glands, Plasma	—do—	—do	—	Peripheral vascular disease, hypertension
Angiotonin	Serum	—	Constriction	Hypertension	Pharmacological tool
Darmstoff	G. I. T.	Stimulated	—	Intestinal motility	—do—
5-HT	Blood, Brain, Intestine	—do—	Constriction except skeletal muscles	Intestinal motility, Noncholinergic C.N.S. Transmitter	Pharmacological tool & for studying MAO activity in man

Plate XVI



FIG. 42. *D. Bovet* Important worker
in the field of antihistaminics and
muscle relaxants.

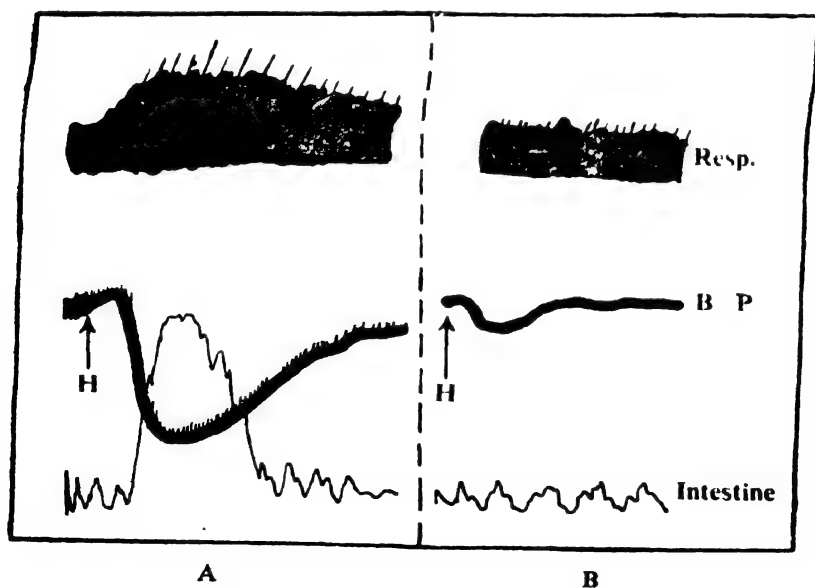


FIG. 43. *Record of respiration, blood pressure and intestinal motility :
Effect of histamine. Left hand (A) before and right hand
(B) after an antihistaminic.*

CHAPTER

16

HISTAMINE, ANTIHISTAMINIC AND ANTIALLERGIC DRUGS

CONCEPTS OF ALLERGY, CHEMICAL NATURE, MECHANISM OF ACTION AND THERAPEUTIC STATUS OF ANTIHISTAMINICS

[As a result of sustained work from a large number of pioneers during the last 50 years, though our knowledge of *histamine* in the causation of *allergic disorders* and the role of antihistaminic drugs, as remedial measures, have been fairly established, there are still many pitfalls in the understanding of this complex problem, of which many essential links for the discovery of specific drugs for different manifestations of allergy, are yet missing. This is further complicated by the fact that of the two types of histamine: (a) *Intrinsic*, formed in the body and acting locally & (b) *Extrinsic*, coming from outside and other tissues, the former is much less amenable to treatment than the latter which responds better to drug therapy.

Histamine, formed by the decarboxylation of the amino acid, l-histidine, in the tissues, is stored in mast and other cells of the body as combined and labile histamine and is released by *antigen-antibody reaction*. In this reaction, if the antibodies are in excess and freely circulating in blood, neutralisation of antigen in the plasma, suspending histamine liberation, would produce a state of *Immunity reaction*.

Histamine is endowed with many pharmacodynamic properties: (a) C-V depression with precipitous fall of B. P. from capillary dilatation, (b) Smooth muscle stimulation, (c) Increased secretions, and (d) Triple response, all due to the direct action of the drug, as also, to the increased tissue permeability. It is a good pharmacological tool and diagnostic agent with hardly any therapeutic application.

With the advancement of this knowledge, ceaseless efforts were made to find out *histamine antagonists*. It was soon found that *physiological* as well as *destructive antagonists*, did not yield fully the desired result. Attention was then diverted to the *competitive antagonists*, which led to the discovery of anti-histaminic compounds, the earlier ones being antergan, and benadryl.

Chemically, the antihistaminics belong to a large number of groups—ethylenediamine, alkylamine, phenothiazine etc. and pharmacologically into the groups of—*Low sedation*—antistine, *Moderate sedation*—pyribenzamine, chlortrimeton, mepyramine and *High sedation*—benadryl, decapryn, phenergan, and also combinations like dramamine, avomine etc.

These compounds show different degrees of specific actions on smooth muscle, skin, secretory functions and in hypersensitivity reactions. Other actions are—CNS depression, local anaesthesia and atropine like actions.

They are dispensed in *special dosage forms*—tablets, injection, creams, ophthalmic solutions and specially coated tablets for *tuned release*. They all have a number of side-effects and act less well on intrinsic histamine. Their *therapeutic efficacy* are still variable, some established, others speculative: (a) Anaphylactic conditions,

(b) Dermatoses, (c) Hay fever and common cold, (d) Motion sickness, (e) Menieres syndrome. (f) Parkinsonism, (g) Drug allergy and blood transfusion hazards. The preparations mostly used are—antistine, chlortrimeton, benadryl, anthisan, avo-mine, siquill and phenargan.]

Histamine and antihistaminic drugs constitute one of the most fascinating studies in modern physiology and pharmacology. During the last 50 years, much work has been done for understanding the role of histamine in allergic disorders and specific remedial measures for combating the same.

The above work is inter-related to the recent advances in fundamental research on a number of naturally occurring substances in the body like 5-HT, angiotensin, bradykinin etc. These substances have been variously described as '*local hormones*', '*autopharmacological agents*' and more recently, as '*autocoids*'. All these agents are considered to be essential for the body for the execution of various functions in health and diseases. Their discovery has also provided newer means for interfering with their action or metabolism by the use of drugs.

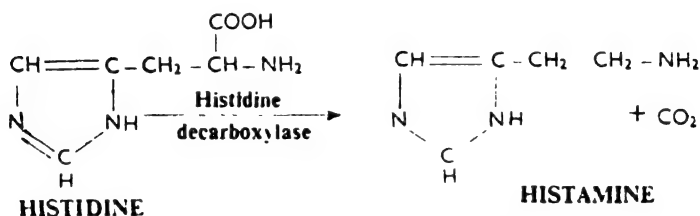
HISTAMINE

Historical. Many have been the workers in the field of histamine and antihistaminic drugs, but amongst the earlier workers, Sir Henry Dale and E. Fourneau have been the pioneers: (a) Histamine was synthesised from *imidazole propionic acid* by Windaus and Vögt (1907), as a chemical curiosity, before its biological significance was recognised. It was isolated by Barger and Dale (1910) from ergot as a contaminant. (b) Experimental anaphylaxis was produced by Dale and Laidlaw (1911) by the injection of histamine into guinea pigs. (c) Triple response was elicited by Lewis (1927), who ascribed it to 'H' substance. (d) Presence of histamine in circulation during anaphylaxis, was detected by Dragstedt (1932) and identified with 'H' substance of Lewis by him. (e) The hypothesis of '*Intrinsic*' and '*Extrinsic*' histamine was introduced by Dale in 1948. (f) Paton and Mac Intosh (1949) showed the release of histamine by drugs and '*Compound 48/80*' was introduced as histamine liberator in 1951.

Source and Distribution. (a) It is widely distributed in plant and animal tissues—stinging nettles (0.1%), wasp venom (2%). It is also present in bee stings and snake venoms and contributes to the erythema, swelling and pain. (b) According to Feldberg, there is hardly any

animal tissue which does not contain histamine. The concentration is particularly high in skin, intestinal mucosa and lungs in mammals i.e., in surfaces exposed to the external environment. (c) Though a considerable amount of histamine is present in food and is also formed by intestinal flora from histidine, it contributes little to the stores of histamine in a body, as most of it is destroyed in liver. (d) Histamine is mostly formed in tissues from histidine by laevohistidine decarboxylase, as evidenced by isotopic studies.

Chemistry. Histamine is β -imidazolethylamine and is formed by decarboxylation of l-histidine, an amino acid.



Illus. VII. Formation of histamine from
l-histidine

For eliciting histamine like activity, the following fragment with ethylenediamine moiety, is essential:



This appears to be necessary for adsorption of histamine on the target receptors for producing the action.

Storage and Forms. (a) The principal site of histamine storage is mast cell, in which, it is present in mitochondria as inactive bound form with heparin. (b) Histamine is released from this protected form when the cells are disrupted. (c) Histamine, stored in mast cells, is not actively metabolised but once depleted, it may take weeks to return to normal levels. (d) It is also present in non-mast cell sites, like skin, GIT mucosa and brain, but the turnover is rapid. The *nascent histamine* is postulated to play the role of 'local hormone'. (e) According to Halpern, histamine is present in the cells at least in two forms:

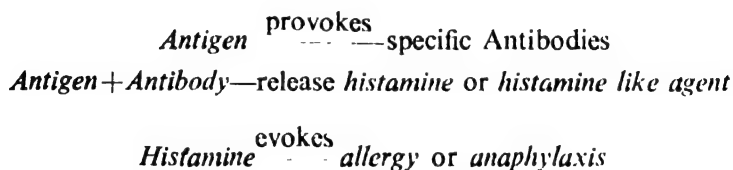
- (i) *Combined histamine*—liberated by tissue destruction and
- (ii) *Labile histamine*—released by physical and chemical stimuli.

Role in Anaphylaxis, Allergy and Immunity. Allergic and anaphylactic manifestations are associated with the release of a large number of

agents like 5-HT, histamine, plasma kinin, slow reacting substance (SRS), etc. Pharmacologically, the histamine concept in allergy has been very fruitful, as, based on this, the antihistaminic drugs have been discovered. The release of histamine in allergic manifestations is evidenced from the following experiments: (a) Guinea pigs, injected I.V. with 0.4-0.8 mg./kg. of histamine or exposed to histamine aerosol, die of anaphylactic shock and bronchoconstriction. A similar reaction on I.P. injection of 10 mg. of egg albumin and the dose repeated after 3 weeks, is also produced. (b) Isolated guinea pig lung, sensitised by egg albumin and perfused with Ringer solution, releases histamine in the perfusate; if egg albumin is added to the perfusion fluid and lung histamine depleted.

In anaphylaxis, there is an explosive type of reaction, due to non-neutralisation of plasma antigens, which get access to the cell antibodies, liberating excess of histamine in plasma and thereby precipitating the shock like condition.

The process, leading to the release of histamine, can be considered to be as follows:



In the above reaction, if antibodies had been in excess and freely circulating in blood, histamine liberation would not occur, because of neutralisation of antigen in the plasma and a state of 'immunity reaction', would follow. In this case, intra-cellular antigen+antibody reaction would not occur.

The effect of pH, temperature and ions on histamine release indicates that an enzymatic process is involved in the antigen+antibody reaction. *Chymotrypsin*, *trypsin* and *phosphatidase A*, have been found to release histamine. It has been postulated that some of these enzymes are implicated in the above process as the release of histamine is blocked by estrases and energy producing enzyme inhibitors, like D.F.P., phenylbutazone, fluoride etc.

An altogether different possibility has also been suggested and it is that the combination of antigen and antibody may evoke some response without the intervention of *humoral agents*. Intravenous administration of antigen-antibody complex has also been found to cause shock like condition without histamine release.

Histamine Liberators. It is evident that the liberation of histamine can be from antigen+antibody reaction, disintegration of tissue cells or activation from proteolytic enzymes. Though it is well known that histamine can be easily released by producing allergic manifestation, the work of Feldberg, Paton, Halpern, Kahlson and others indicates that this is also possible by introducing a number of chemical agents, now known as '*histamine liberators*'. These agents are capable of releasing histamine from tissue-bound form with minimal injury to cells.

HISTAMINE LIBERATORS

Sensitising agents	Antigens—pollen grains, dust particles.
Traumatic agents	Toxins, venoms.
Proteolytic enzymes	Chymotrypsin, trypsin.
Surface active agents	Detergents, Tween-20
High molecular-weight substances	Egg-albumin, horse serum, peptone, dipeptides.
Alkaloids	Tubocurarine, morphine, atropine.
Diamidines	Stilbamidine, propamidines.
Quaternary salts	Mytolon, suxamethonium.
Polymers	48/80, dextran, polyvinyl, pyrrolidone, compound 19/35 L.
Vegetable drugs	Cowhage, marking nut.

Intrinsic and Extrinsic Histamine. Incomplete antagonising action of antihistaminics in histamine disorders, has led to the concept of the possibility of "*intrinsic*" and "*extrinsic*" *histamines*. The former is released intracellularly and act locally while the latter, is present in circulation, either from injection or from remote organs. On elucidating the actions of antihistaminics on these two types of histamine, it became evident that: (a) Antihistaminics counteract better, anaphylaxis evoked by intravenously injected histamine than one, evoked by antigen, (b) Exogenous histamine, circulating in blood, is better counteracted than endogenous histamine, released intracellularly.

This is why antihistaminics are more effective in *hay fever* and *urticaria* than in *asthma*, where the antigen+antibody reaction takes place in the cells of bronchial muscles, resulting in liberation of histamine intracellularly.

Histamine Analogue. *Butazole hydrochloride* stimulates gastric secretion like histamine, without evoking the other responses of the latter. It is used for gastric function test. *Dose:* 0.5 mg./kg. I.M.

Metabolism. It is readily absorbed from the site of injection and rapidly metabolised in the body. It is poorly absorbed and mostly

destroyed locally after oral administration. There are two major paths of histamine detoxication in man: (a) Histamine is converted to methyl histamine by imidazol-N-methyl transferase, which is partly catabolised to methyl imidazol acetic acid, mainly through mono amine oxidase. More than half of the injected histamine appears in this form. (b) Histaminase or diamine oxidase, which is present in most of the tissues, is responsible for the oxidation of remaining histamine with the production of imidazol acetic acid and its ribose, and excreted in urine. (c) Small quantity of acetyl histamine in urine may be the result of conjugation in liver and intestine by acetylating enzyme.

All these processes take place with a degree of rapidity and therefore histamine action is of short duration. None of the histamine metabolites are pharmacologically active.

Actions. Histamine is involved in gross physiological and pharmacological reactions, which are more of toxic than therapeutic importance. Actions on cardiovascular system, exocrine glands and smooth muscles are considered to be of paramount importance. There is a wide variation in susceptibility to histamine in different animals. Histamine is very dangerous to man even if injected in low doses due to various degrees of susceptibility. Important actions of histamine are as under:

C.V.S. (a) Precipitous fall of B.P. to shock level, due to extensive capillary dilatation, except in rabbits and guinea pigs. (b) Constriction of pulmonary artery in rabbit and of interlobular hepatic vein in dog. (c) Capillary dilatation antagonised by adrenaline and atropine, and only partially by antihistaminics. (d) Brisk dilatation of cerebral vessels, causing histamine headache in man.

Smooth Muscle: (a) Histamine action is a direct one and not antagonised by atropine. It may be due to an influx of calcium or depolarisation by potassium. (b) Uterus, intestine and bronchioles are stimulated but in therapeutic doses, no significant oxytocic action in women is observed.

Exocrine Glands: (a) Histamine is a powerful gastric secretagogue, increasing the output of both pepsin and acid. The action is not antagonised by antihistaminics. (b) It has some stimulant action on salivary, pancreatic, intestinal, bronchial and lacrimal secretions.

Respiration. Extreme degree of broncho-constriction resulting in *experimental asthma*, antagonised by adrenaline and aminophylline, but not by atropine and antihistaminics.

Skin. Typical urticarial response on intradermal administration,

known as "*triple response*" comprising of (a) localised red spot, (b) extended red flare and (c) local oedema, forming a wheal. This is due to capillary dilatation, as well as, increased cellular permeability.

Adrenal Medulla. Histamine causes release of *catecholamines* from the chromaffin tissue, leading to the rise in B.P. and hyperglycaemia. This action is sometimes used as a diagnostic test for *phaeochromocytoma*.

Other Actions. such as on the tissue growth, neurotransmission and reproduction, are mostly of scientific curiosity.

Therapeutic Uses—mostly diagnostic:

(a) *Gastric Acidity test* for diagnosis of *achlorhydria*. Dose: 0.25-0.5 mg. S.C.

(b) *Axon Reflex Test*: after histamine injection, normally, vasodilatation through an axon reflex. This indicates the integrity of sensory nerves in neurological conditions and leprosy.

(c) Measurement of *circulation time*: interval between I.V. injection and flushing of face. Also wheal formation after S.C. histamine inj., a test for circulatory competency in extremities.

(d) Diagnosis of *phaeochromocytoma*: histamine 0.05 mg. should produce a fall in B.P. in normal persons and in essential hypertension. A rise in systolic B.P. by 100 mm. Hg., which is due to stimulation of the adrenal system, is indicative of *phaeochromocytoma*.

(e) Histamine binding or histaminopexic power of the plasma is reduced in allergy and this is used as a clinical test for the diagnosis of allergic disorders.

Histamine thus, has manifold pharmacodynamic actions and it seems to be responsible for the production of allergic and anaphylactic reactions.

Since 1930, it has been the endeavour of chemists and pharmacologists to find out specific drugs for histamine disorders, which has resulted in the discovery of '*antihistaminics*', discussed hereafter.

ANTIHISTAMINICS

With the advances in modern concepts of drug action, it became evident that neither '*physiological antagonists*' like *adrenaline*, nor '*destructive antagonists*' like *histaminase*, could specifically combat the effects of histamine produced by allergy. It was soon conceived that '*competitive antagonists*', blocking histamine receptors would probably produce the desired effect, on the basis of *biological antago-*

nism. The acceptance of this relationship led to the rapid development and therapeutic exploitation of many antihistaminics during the last few decades.

Historical. (a) The discovery of potent antihistaminic drugs started in 1937 with the work of Fourneau, Bovet and their colleagues. (Plate XVI) (b) Ungar, Parrot and Bovet, while examining the action of sympathomimetic and lytic substances, observed that compounds which blocked the action of adrenaline on isolated guinea pig intestine, did not necessarily block the action of histamine and *vice versa*. (c) Phenolic ether, like *benzdioxane*, on the contrary, showed both adrenolytic and histaminolytic properties. (d) The synthesis of other analogues led to the development of *antergan* by Halpern, *mepyramine* by Bovet and *benadryl* by Loeu, during 1942-46. (e) Useful knowledge about structure-action relationship, coupled with the enthusiasm of clinicians and public, encouraged the introduction of new antihistaminics, nearly 50 of which, are now available for use, claiming advantages over the original compounds.

Evaluation. Some of the pharmacological actions of histamine have been utilised for the evaluation and comparison of antihistaminic drugs:

(a) *In vitro* effect on smooth muscle: Classical 'Magnus technique' with isolated guinea pig ileum, to find out the inhibition of histamine induced contractions.

(b) Survival of guinea pigs from bronchoconstriction, induced by intravenous or aerosolised histamine after oral administration of antihistaminics. With *neoantergan* (0.05 mg./kg.), survival time is 30 min. 2 mins, in the control.

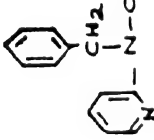





(c) Protection of guinea pigs or mice against intraperitoneal egg albumin induced anaphylactic shock or dextran and 48/80 compound reactions, by oral or S.C. administration of antihistaminics.

(d) Study of the antagonising or blocking action of antihistaminics against histamine induced fall of B.P. in cats or dogs.

(e) Protection against local triple response, induced by intradermal injection of histamine in man and various animals.

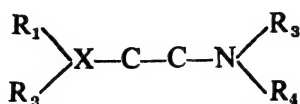
(f) Histological determination of the protection of mast cell damage, in sensitised rats, after prior treatment with antihistaminics.

Chemistry. This is extremely complicated and shows little structural relationship with histamine. A true conception of substrate competition cannot therefore be had on the lines of PABA and sulpha drugs.

Group	Nature of X	Formula	Drugs
Ethylenediamine	N	 $\text{N} - \text{CH}_2 - \text{C}_6\text{H}_5$ <p><u>PYRIBENZAMINE</u></p>	Pyribenzamine Antistine Chlorothane Neo-antergan Histadyl
Amino alkyl ether	O	 $\text{O} - \text{CH}_2 - \text{C}_6\text{H}_5$ <p><u>BENADRYL</u></p>	Benadryl Ambodryl Oranamine Decapryn
Alkylamine	C	 $\text{C} - \text{CH}_2 - \text{CH}_2 - \text{N}(\text{C}_6\text{H}_5)_2$ <p><u>CHLOR TRIMETON</u></p>	Trimeton Chlor trimeton Actidil
Piperazines	C	 $\text{C} - \text{CH}_2 - \text{CH}_2 - \text{N}(\text{C}_6\text{H}_5)_2$ <p><u>CYCLIZINE</u></p>	Cyclizine Chlorcyclizine Meclizine
Phenothiazines	N	 $\text{N} - \text{CH}_2 - \text{C}_6\text{H}_5$ <p><u>PROMETHAZINE</u></p>	Promethazine
Miscellaneous	—	 C_6H_5 <p><u>THEOPHORIN</u></p>	Theophorin

However, as information about full knowledge of metabolism of antihistaminics is not available, their structural similarity, after biotransformation, cannot also be postulated.

Most of the active antihistaminics are represented by the general structural formula:



where R_1 and R_2 are benzene or heterocyclic aromatic rings and X is—oxygen (benadryl), nitrogen (pyribenzamine) or carbon (chlorpheniramine) connecting the side chain to the nucleus. In all the three, there is a secondary or tertiary nitrogen in the side chain, where R_3 and R_4 are mostly methyl groups. Antihistaminics can be classified into various groups on the basis of the nature of X, shown above.

Classification. Antihistaminics are conventionally classified on the basis of *sedation*, which is a constant side-effect of this group of drugs. In many cases, the degree of sedation and intensity of antihistaminic action, are related.

<i>Sedation</i>	<i>Name of Drugs</i>
Low	Antistine, neohetramine, theophorin, histantin, synopen, chlorpheniramine.
Moderate	Pyribenzamine, chlorithen, chlortrimeton histadyl, mepyramine, trimeton, ambodryl.
High	Benadryl, decapryn, phenergan.

Metabolism. (a) Rapid absorption from G.I.T. and site of injection; peak tissue level in one hour, disappearing in six hours. Degradation mainly in liver. (b) Excreted by kidney, mostly degraded but partly unchanged. Urinary metabolic products are mostly hydroxy derivatives, conjugated with glucuronic acids.

Actions. The pharmacodynamic effects of antihistaminics may be considered under two headings: (a) Specific antagonistic action against histamine. (b) Other non-specific actions.

Specific Actions. Antihistaminics act antagonistically on the following structures.

(a) *Smooth muscles:* Effectively antagonise the stimulating actions of histamine on segments of G.I.T., uterus, larger blood vessels and bronchial muscle. Feeble action against broncho spasm, induced

by intrinsic histamine, liberated by antigen-antibody reaction and therefore not effective in asthma.

(b) *Secretory glands*: No effect on gastric secretion, induced by histamine. Secretions of salivary and other exocrine glands reduced.

(c) *Skin*: The triple response of histamine is modified or blocked. Wheal formation, flare and itchings are checked. Local application is more effective than systemic administration.

(d) *Hypersensitivity, allergy and anaphylaxis*: Oedema and itching are well controllable, but little effect against hypotension and no effect against gastric secretion. Bronchoconstriction in anaphylaxis is poorly antagonised.

Other Actions. *C.N.S.*—two types of responses:

(a) Depression of cortex and lower centres—relief of motion sickness and parkinsonism, due to the depressant action on medulla and extrapyramidal systems, respectively.

(b) Stimulation of *C.N.S.*, after rapid *I.V.* injection—evidenced by restlessness, nervousness and insomnia. Epileptiform convulsions in patients with focal lesions of cerebral cortex. Convulsions sometimes occur in antihistaminic poisoning.

Local Anaesthetic Action. Most of the antihistaminics show some degree of local anaesthetic action and some are even more potent than procaine. Incidence of irritation and possibility of sensitization, limit their use.

A.N.S. Atropine like activity—producing dryness of mouth in some patients.

Cardiovascular System: No significant action on B.P. In higher doses, quinidine like action on myocardial conduction, conferring antifibrillatory property to these drugs.

Smooth Muscle: Mild spasmogenic action on bowel, uterus and bladder, causing occasional gastro-intestinal complaints and dysuria during antihistaminic therapy.

Mechanism of Action. Histaminic synthesis, release and inactivation are not modified nor its actions physiologically antagonised. Antihistaminics occupy the receptors of the effector cells, prevent the access of histamine and thus block its action.

They produce reversible union with a common receptor without eliciting their own action at the site. The action thus, is '*competitively antagonistic*'.

Toxicity. The antihistaminics are relatively non-toxic at usual dose

levels, though minor side effects are not uncommon: (a) C.N.S. depression, ranging from mild sedation to hypnosis. (b) Nausea, headache, vertigo, xerostomia restiveness, G.I.T. distress, C.V. disturbances, leucopenia, dysuria and convulsions in children. (c) Hypersensitivity reaction—dermatologic complications and skin eruptions, sometimes after oral administration but more often from local applications. (d) In acute poisoning, nervousness, tremors, muscle twitching, delirium and convulsions, followed by respiratory depression and unconsciousness.

Preparations

(1) *Benadryl* (diphenhydramine):

(a) *Capsule* 25 or 250 mg., *Elixir* 2.5 mg./ml., *Inj.* 100 mg. 10 ml. *Cream* 2%.

(b) *Special points*: (i) *High sedation* in 50% of cases, (ii) Use in *Parkinsonism* and motion sickness and as an expectorant.

(2) *Pyribenzamine* (tripelennamine HCl):

(a) *Tablet* 25 or 50 mg., *Elixir* 30 mg./dr., *Inj.* 25 mg./ml. *Ointment* 2%.

(b) *Moderate side effects* in 25% cases, *moderate sedation* and therefore widely used.

(3) *Mepyramine maleate* (anthisan or neoantergan):

(a) *Tablet* 25 or 50 mg.

(b) *Special points*—*Long duration of action* with moderate sedation. *Side effects* only in 20% cases.

(4) *Promethazine HCl* (phenegan):

(a) *Tablet* 25 mg. 14 times more potent than meparymine. Duration of action 32 hours.

(b) *Special points*—*local anaesthetic effect* with reduction in capillary permeability.

(5) *Antistine* (antazoline):

(a) *Tablet* 100 mg. b.i.d., *Ophthalmic solution* 0.5%.

(b) *Special points*: Mild action, low sedation, less toxicity and tissue action.

(c) *Incidence of reaction* in 20% cases.

(6) *Dramamine*:

(a) Combination of *benadryl* 54% + *theophylline*, 46%. Available as *tablets* of 50 mg.

(b) *Special points*: *antiemetic* with *high sedation* and also *atropine* like actions.

(c) Used in *motion sickness* in 50 mg. Q.D.S.

(7) *Avomine* (promethazine 8 *Chlorotheophyllinate*).

- (a) *Tablet 25 mg. Prophylactic as well as therapeutic use in travel sickness. 25 mg. tab. 2 hr. before commencement of journey.*
- (8) *Chlorpromazine (largactil):* The name derived from 'large spectrum of activity and is a potent *antiemetic* and *tranquilliser* but a *weak antihistaminic*. Dose 25-50 mg./Os.
- (9) *Chlortrimeton maleate (chlorpheniramine maleate) (piriton).*
- (a) *Tab. 4 mg./OS, QDS; Sol. 0.5 mg/ml.*
- (b) *Potent antihistaminic and side effects in only 10% cases.*
- (10) *Trimeton*
- (a) *Tablet 25 mg., Elixir for children and Cream 3%.*
- (b) *Incidence of side reactions in 15-20% of cases.*

Choice. difficult, due to the availability of a very large number of compounds and thus '*trial and error method*' is common, the underlying principle of choice being (a) Minimum sedation and maximum therapeutic effect, (b) Minimum side-effects.

Bearing these points in mind, the trend of clinicians in the use of antihistaminic is often limited to (a) Antistine for low sedation and low toxicity. (b) Piriton—for cheapness, and (c) Benadryl for stronger anti-allergic action and sedation.

Drug combinations like antihistaminics—stimulant or decongestant or analgesic, for palliative treatment of allergy and milder forms of upper respiratory tract diseases, are not only available but often used. Antihistaminics, combined with anti-inflammatory steroids, are used for more serious allergic or asthmatic conditions.

For prolonged action, '*time released dosage forms*', are preferred. Some of these, *permit* 50% for quick absorption and remaining 50% for slower release, thus permitting immediate as well as prolonged action, as in the case of special preparations of *piriton*, *chloririmetone* and *dibistine*.

Therapeutic Uses. Though specific for allergic disorders: (a) *Some are established.* (b) *Others still speculative.*

Acute anaphylactic shock: antihistaminics + sympathomimetic amines are sometimes life-saving. Antistine I.M. as prophylactic but when shock has set in—*adrenaline* is the drug of choice. Antistine or piriton injections are commonly used.

Dermatoses: (a) Most effective in acute and chronic urticaria and angioneurotic oedema. with 80% result. In chronic dermatitis piriton, benadryl or anthisan cream may be tried. Improvement in 50% cases. Good results are also obtained in insect bites, stings and pruritis and

contact dermatitis. Topical application is preferred, but prolonged use may result in the *sensitisation of skin*.

Hay fever: (a) Good result and relief in 60-80% of cases. (b) Systemic administration, as well as, antistine+pristine intranasally. (c) Method of desensitization of Besredka against specific antigen.

Asthma: (a) Palliative in about 30% of mild cases only, where allergic component is the chief factor. (b) Ephedrine, isoprenaline, aminophylline and adrenocorticoids, still remain sheet anchors.

Common cold: No definite place, relieves congestion and secretion. Commonly used drugs are benadryl, piriton and synopen.

Motion sickness and vomiting: Dramamine and avomine are specially indicated, as they are sedative for chemoreceptor trigger zone and give less side effects.

In '*Meniers' syndrome*, in which there is labyrinthine disturbances with peculiar dizziness, vertigo, reeling of the surrounding objects, and vomiting, some of the antihistaminics and aspirin are helpful palliatives.

Parkinsonism. Already discussed.

Blood transfusion. Injectable antihistaminics like piriton, colithene are useful for preventing allergenic, pyrogenic reactions, if given simultaneously.

Drug Allergy. This is an annoying episode which seems to be on the increase, in recent times. Sensitivity of a person, nature of a drug and overdosage, are the important contributory factors. This reaction is on the increase with the advent of newer potent drugs.

Drug allergy is more common with higher molecular weight substances but a simple compound like aspirin can produce allergic reaction, in which case, combination with serum protein act as allergen. It has been seen with practically all group of drugs but is more common with :

- (a) Antibiotics—penicillin, streptomycin, bacitracin.
- (b) Chemotherapeutic drugs—sulphas, quinine, arsphenamine.
- (c) Analgesic-antipyretics—aspirin, salicylates, amidopyrine, cinchophen.
- (d) Protein preparations—sera, vaccine, whole liver extract, heparin, enzymes.
- (e) Miscellaneous—bromide, procaine, mercurial diuretics.

The reactions vary from mild to severe shock and collapse and include:

- (a) Skin reactions—mild rash, urticaria, dermatitis and itches.
- (b) Systemic reactions—drug fever, angioneurotic oedema, rhinitis, asthma, anaphylactic shock, nitritoid crisis, hepatic necrosis, etc.

Management. (a) Prophylactic—antihistaminics *piriton* and *avil*. (b) During attack—adrenaline, cortisone, antihistaminic and calcium gluconate.

The role of *cortisone* in allergic disorders, not responding to antihistaminics, is important, though its exact mechanism of action is not established. May act by (a) Decreasing release of endogenous histamine, (b) Protective umbrella mechanisms, (c) Increased resistance of target cells.

THERAPEUTIC ABSTRACT

<i>Bronchial asthma</i>	<i>V.M. rhinitis, Hay fever, Common cold</i>	<i>Urticaria, Serum sickness Ang. neuro. oedema</i>	<i>Allergic dermatitis, Pruritis, Eczema</i>	<i>Migraine Parkinsonism Travel sickness</i>	<i>Drug allergy</i>
Benadryl, Chlortrimeton Promethazine	Any but Antistine + privine as nasal drops	Any	Anthisan or Antistine cream or tablets	Drama- mine, Bena- dryl, Deca- pryn, Avomine	Phenargan, Antistine, Anthisan or any other

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SECTION
V
CENTRAL AND PERIPHERAL NERVOUS SYSTEM
CHAPTER
17
GENERAL CONSIDERATIONS OF THE NERVOUS SYSTEM
PHYSIO-PHARMACOLOGICAL CONSIDERATIONS

[In view of the greater complexities of the CNS, appropriate analysis of drug action without undergoing a risk of overlapping, is difficult. Cerebrum, basal ganglia, thalamus, hypothalamus, medulla and spinal cord, all pose the same problem. Other recent concepts of the reticular formation, blood-brain and blood-aqueous barrier as well as the role of neuro-hormones in producing actions of certain pattern—excitatory or inhibitory, have thrown newer lights in our understanding of the intricate mechanisms of drug action and their limitations.

In the light of these developments, it is becoming increasingly clear that CNS drugs produce different patterns of action, even in a generalised manner, : (a) *Non-selective stimulation*, (b) *Nonselective depression*, and (c) *Selective modification*, each one of which, would again have many variants. In this manner, we have to understand the nature of action of different groups of CNS drugs—the *analeptics*, *anaesthetics*, *hypnotics*, *tranquillisers*, *antiepileptics*, *antitussives*, *antiemetics* as well as *narcotic* and *nonnarcotic analgesics*, many of which also act in continuum, one action changing to another, according to the doses used. The newer techniques including psychopharmacological and EEG studies are gradually throwing more and more light on the intricate working of drugs on this system.]

Unlike autonomous nervous system, the study of central nervous system drugs is infinitely more complex. Scientific analysis of drug actions, their seat, mechanism and interrelation are, therefore, much more imperfect. Further, the actions are not often selective but overlapping and full of side-effects. It is seldom localised but often spreads to other structures producing complex and even opposing actions. It is not therefore, easy to pin-point many of the actions due to the insufficiency of knowledge of structure and function of all the areas and tracts in this system.

Physio-Anatomical Considerations. Of the various component parts of the brain, the *grey matter* deserves a special reckoning. It represents only 1% of the total body-weight but gets 10% of cardiac output and O_2 (5 ml of O_2 /G/h and 1-2 ml of blood/G/min). It has thus a very high metabolic rate and any anoxic state causes irreversible damage and death within a brief period—(i) Pyramidal cells—8 mts, (ii) Cerebellar fibres—13 mts, (iii) Medullary centres—20 mts, (iv) Sympathetic ganglia—3 hours.

Divisions. Several approaches—*Anatomically*—cerebrum, cerebellum medulla, cord, each of these again, into distinct tracts and nuclei. *Functionally*—sensory, motor, memory, association and regulation of autonomic functions. From *evolutionary* standpoint, respiration and motor reflexes are *primitive* in nature, while movements and higher activities, are phylogenetically *newer*. None of these systems however, operate independently but they interact. Drug action also is seldom neuronal.

Anatomical classification, detailed hereafter, appears to be the most satisfactory.

Cerebrum. Besides other functions, it is primarily concerned with consciousness, conditioned reflexes, correlation of incoming sensory with outgoing motor responses.

Basal Ganglia. masses of grey matter within the white matter of cerebrum and include the corpus striatum. They help in the regulation of muscle tone and integration of automatic and somatic motor functions.

Thalamus. Primitive receptor and relay centre for sensory impulses, producing crude awareness—indiscriminating type of consciousness.

Hypothalamus. Higher centres for controlling A.N.S. and homeostatic functions—body temperature, water balance, CH and fat metabolism and sleep.

Mid Brain, Pons and Medulla. These constitute the brain stem and contain nuclei of cranial nerves and the ascending and descending tracts. The medulla oblongata is termed as the “*vital node*” and the important centres which lie in this area are—*respiratory*, *cardio-inhibitory* and *accelerator*, *V.M.*, *deglutition*, *vomiting* and *cough*.

Red Nuclei. Located in the mid brain and help in the regulation of muscle tone and coordination.

Cerebellum. concerned with the maintenance of equilibrium.

Spinal Cord. serves as a centre for reflex activities and is traversed by a series of *tracts* which carry the impulses either to or from the brain, as ascending and descending pathways.

Ascending (a) *Fasciculi gracialis* and *cuneatus* in posterior column carrying kinaesthetic and refined tactile impulses, to reach consciousness. (b) Dorsal and ventral *spinocerebellar tracts*—for unconscious muscle senses. (c) Lateral and ventral *spino-thalamic tracts*—for pain and temperature and crude tactile sensitivity, respectively.

Descending (a) Lateral and ventral *cortico-spinal tracts*—for voluntary control of striated muscles. (b) *Rubrospinal* and *Reticulospinal*—for involuntary control of striated muscles.

Reticular Formation and Concepts of Consciousness. (a) This is a new concept which has been based on extensive work, carried out on the reticular or centrencephalic system, by steriotaxic techniques. (b) It has a functional significance for the activity of brain as a whole, with regard to consciousness and integration. (c) The reticular system has *ascending* and *descending* portions and is anatomically divided into different parts—*formatio-reticularis*, *tegmentum*, etc. (d) The system activates the cerebral cortex as a whole and this is known as “arousal” or “state of alertness”. This is opposed to *sleep* and *unconsciousness*. (e) Sensory impulses are analysed here and efferent responses decided upon. Degree to which efferent impressions are fixed on these centres, determines the state and degree of consciousness. (f) Drugs which diminish the threshold for consciousness, act as stimulants, while those which raise the threshold, act as sedatives and hypnotics.

Blood-Brain Barrier. It is a physiological barrier between (a) Brain cells and surrounding capillaries, (b) Blood in the choroid plexus and C.S.F.

The barrier is due to the selective permeability of capillaries in brain and the choroid plexus. It is a protective mechanism for brain cells against toxic substances.

The barrier is of *lipoidal nature* and whether a drug will pass through it or not or the degree and extent of passage, will depend on the following factors:

- (a) Blood level of drugs—higher the blood level, higher the diffusion.
- (b) Binding to plasma proteins.
- (c) Presence of meningeal inflammation.

(d) Physico-chemical characteristics—molecular size, solubility. Lipoid soluble substances are highly diffusible and undissociated molecules are better penetrating than others.

Those drugs which diffuse slowly, also leave the brain slowly, while, those which cross the barrier easily, are also excreted equally quickly.

From their degree of diffusibility, drugs constitute *three* distinct groups:

COMPLETELY DIFFUSIBLE Ethyl alcohol, paraldehyde, alkaloids, sulphadiazine

INCOMPLETELY DIFFUSIBLE Iodides, bromides, pentavalent arsenicals

NONDIFFUSIBLE Neocarsephenamine, trypan blue, ferrocyanide

Amongst the antibiotics, *penicillin* is least diffused, *streptomycin* better and *Isonex* still better. Broad spectrum antibiotics have satisfactory diffusion. This is also true for *blood-aqueous humour-barrier*, in respect of these drugs.

Types of Central Actions

Excitation. Basic mechanism of action potential is the same as in the peripheral system—by release of transmitter and depolarisation. When excitatory polysynaptic potential (E.P.S.P.), reaches a critical level in the pre-ganglionic neurones, action potential arises in the post-ganglionic neurone.

Inhibition. Presynaptic and postsynaptic systems are present, side by side, in the same system.

Neuro-Hormones. Not definitely established but it is believed that these may be (a) Acetylcholine, (b) 5-hydroxytryptamine, and (c) Gamma aminobutyric acid (GABA).

Pharmacological Considerations. Drugs acting on the C.N.S. act in different manners.

I. General non-selective stimulation. In this, according to dosages used, practically all the parts of the C.N.S. are more or less involved. The analeptics, detailed in the next chapter—strychnine, picrotoxin, coramine, leptazol, sympathomimetic dextedrine and xanthenes belong to this category. Though their effect is usually non-selective but not without some predilection for certain areas (cortex, medulla or cord). Some of them act directly (leptazol), some reflexly (coramine),

a few specifically (magimide and nalorphine) and some (strychnine) by the blockade of inhibition mechanism. These actions, though of general nature, are still often complex and in higher dosage, the stimulation may lead to complications like convulsions, not infrequently.

II. General non-selective depression. This refers to a very large array of drugs—general anaesthetics, hypnotics, sedatives and narcotics, all of which, while possessing the general property of C.N.S. depression, show special characteristics for clinical uses.

The group which produces loss of consciousness and sensation and also muscular relaxation, is known as *general anaesthetics*. The group which quietens the agitated patients and stops convulsive seizures are known as *sedatives*; those which produce hypnosis, resembling normal sleep, are known as *hypnotics*. Depending on whether this last group, also relieves pain or not, it is subdivided into anodyne and non-anodyne hypnotics.

Between these, there is a third group—ethanol and morphia which besides C.N.S. depression and relief of pain, induce *habit formation* and are consequently known as *narcotics*.

There is another group of drugs which has come into prominence in recent years under the heading "*Psycho-pharmacological drugs*", used for the mentally ill. With the advances in pharmacology, it is now possible to induce thinking disturbances and hallucinations with a group of potent pharmacological tools, known as "*hallucinogens*" and remove these disturbances and clear up the mind with "*ataractics*" and finally improve the depressed states of mind with "*mood elevators*". All these drugs act on the important vital areas of the hypothalamus and the ascending reticular formation and their action in therapeutic doses, is not to sedate nor hypnotise the patients but tranquillise them.

III. Selective modification. In contrast to the above, there are a number of other groups of drugs, the pattern of whose actions is not generalised depression, nor depression of wider areas, but is more on selective areas. These may be considered of to be "*selective depressants*" as opposed to non-selective ones, referred earlier.

They are: (a) antitussive, (b) antiepileptic, (c) analgesic-antipyretics. The first sedates the cough centre and relieves cough by various mechanisms. The antiepileptics depress the motor cortex and block the spreading of cerebral discharges. The analgesic-antipyretics constitute 2 distinct groups—one possessing antirheumatic, antigout and uricosuric action and the second showing antipyretic effect of a general nature with less analgesic effect. They are used in cases of hyperpyrexia for reducing the temperature of any origin.

Lastly, there is also a group of drugs which selectively depresses

the sensory nerve endings, though not the C.N.S. and along with general anaesthetics, they are also useful for surgical intervention. For the sake of convenience and for understanding the scope of different anaesthetic measures for operative surgery, they will also be considered here as "*local anaesthetics*" along with their counterparts.

However, the above approach could not but be somewhat arbitrary as these various groups of drugs do not work in watertight compartments and anyone of them has more than one action and one use e.g. the barbiturates not only act as sedatives but as hypnotic, antiepileptic and also as general anaesthetics. Similarly, alcohol and morphia, in higher doses, can induce a hiatus of brain but because of their low safety margin between anaesthetic and lethal effect, they cannot be considered for general anaesthesia purposes.

The position, outlined above, is summarised, in the following table:

C.N.S. depressants—non selective producing unconsciousness and loss of sensation.	General anaesthetics
Peripheral sensory depressant—selective, producing loss of sensation but no unconsciousness	Local anaesthetics
C.N.S. depressants non selective and non anodyne producing sedation and hypnosis.	Sedatives, hypnotics & anti-Convulsants
C.N.S. depressants non selective, non-analgesic and habit forming.	Alcohol
C.N.S. drugs acting on hypothalamic areas and used as pharmacological tool and in mental illness producing (a) hallucination, (b) removing thinking disturbances and (c) elevating mood in depressed conditions.	(a) Hallucinogens (b) Tranquillisers (c) Mood elevators
Selective depressants of motor cortex and adjacent areas producing anti-convulsant and anti-epileptic actions.	Antiepileptics and anti-con- vulsants
C.N.S. depressants having both selective and non selective actions, producing marked drug habit and acting as analgesic hypnotic.	Morphine
Selective depressants of cough and vomiting centres and acting both centrally and peripherally.	(a) Antitussive expectorant and (b) Anti emetic drugs
Selective depressants of pain and thermoregulatory centres with doubtful peripheral actions (a) analgesic, antiinflammatory & uricosuric drugs; (b) antipyretic—predominantly of a general and not specific type with mild analgesic effect.	(a) Antirheumatic & antigout drugs (b) General antipyretics

Character of Action. '*Action in continuum*'.

(a) Tranquillisation→Sedation→hypnosis→anaesthesia→coma.

(b) Mild hyperexcitability→moderate→ & severe convulsions.

As patterns of action of each drug, *excitatory* or *inhibitory*, differ, drug antagonism also is not complete. Further, excessive stimulation is followed by exhaustion and depression but the opposite is not correct.

Basis for Drug Selectivity. Drugs are not general stimulants and depressants but often produce a constellation of actions and also side-effects, which also can sometimes be therapeutically exploited: "One man's side-effects is another man's remedy". The riddle of selectivity therefore remains often unsolved and the following postulations are offered: (a) Selective localisation exists but not to the extent of a concerned neurone. (b) Differential action on different cells—imagined but not proved. (c) Differential action depending on neuronal organisation—depressants act better on polysynaptic chains. (d) Differential action depending on the functional state of neurones—action of antipyretics in hyperpyrexia and psychic drugs in mental disorders. (e) Differential action of drugs on neuronal metabolism—nutrition and use of metabolites. This may affect their excitability. (f) Differential action through neurohormonal transmitter mechanism is not as much known as in the case of A.N.S.

Limitations. Inadequacy of drug efficacy, toxicity, multiple actions, side effects and lack of specific drugs—are the present hurdles.

ANALYSIS OF ACTIONS

CAFFEINE	From small doses, a mild stimulation of higher centres and in large doses stimulation of respiratory centres and even convulsions.
ALCOHOL	Depression of reticular formation and inhibitory centres but in large doses, depression of respiratory centres.
ANAESTHETICS	Depression of sensory and motor areas and also of reflex centres but in large doses, the respiratory centres are also depressed.
PHENOBARBITONE	Both the sensory and motor areas are depressed.
DILANTIN	Only depresses the motor area of the cerebrum.
METRAZOL	Stimulates motor area and also the respiratory centre in large doses.

ANALGESICS	Act only on the thalamus and spare the cortex. Morphine acts on the sensory cortex and also depresses the respiratory and cough centres.
MESCALINE & LSD ₂₅	Produce thinking disturbances even in small doses.
SPINAL ANAESTHETICS	Block spinal nerves, affecting both motor and sensory pathways.
STRYCHNINE	Affects the cells of dorsal and ventral horns in small doses with restricted action. In large doses, the action ascends to the medulla.
CURARE	Though stimulant of cord, causes a neuromuscular block peripherally.
PHENANTHRENE ALKALOIDS	Increase excitability of the cord.

Methods of Study. Many but often *qualitative* and far from satisfactory.

1. *Tests for loss of consciousness*—as in the case of general anaesthesia—along with loss of sensation, reflexes and muscle tone.
2. *Acuity tests*—*Pain intensity test* by analgesiometry and also by Wolff-Hardy-Goodall Technique.
3. *Mental*—Typing, calculation and shooting tests—for determining speed and accuracy.
4. *Motor function tests*—Hoffman-Maize Technique for briskness of reflexes.
5. *Psychopharmacological tests*—Skinner-Box, Pole climbing and pecking reflexes and lastly
6. *E.E.G. Studies*—based on the recording of potential changes in different parts of the brain with a highly sensitive E.E.G. machine. From different types of tracings due to different types of waves, conclusions are drawn :
 - (a) α waves—5-15/Sec—present at rest. γ waves—50/Sec—present during mental activity, slow delta waves—4/Sec—present in sleep, coma and also after Alcohol and Insulin.
 - (b) In convulsive and epileptic conditions α waves disappear, in petitmal domek spike type of pattern.
 - (c) Stimulants and depressants of C.N.S. produce different patterns of tracing and even difference in design of waves is observed with general anaesthetics and hypnotics.

This technique is an useful diagnostic aid for detection and localisation of brain tumours and also for study of drug actions on C.N.S.

Plate XVII

SOME CENTRALLY ACTING MEDICINAL PLANTS

FIG. 44. *Strychnos nuxvomica*FIG. 45. *Cannabis indica*FIG. 46. *Papaver somniferum*FIG. 47. *Erythroxylon coca*FIG. 48. *Rauwolfia serpentina*

Plate XVIII

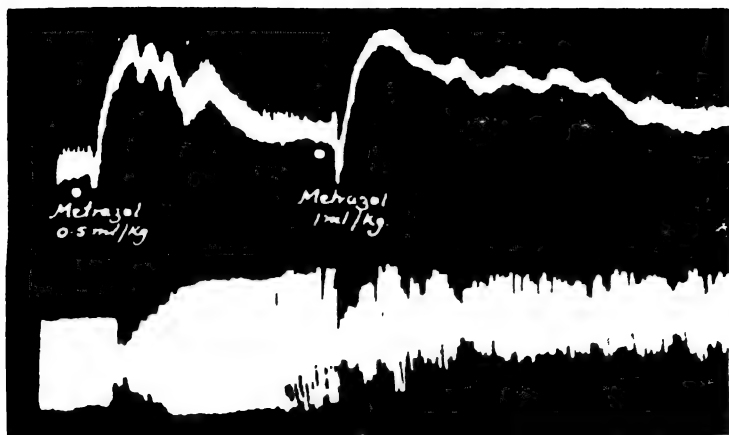


FIG. 49. *Dog blood pressure* : note the respiratory and vasomotor stimulation after metrazol.



FIG. 50. Effect of picrotoxin and nikethamide on morphine induced respiratory depression.

CHAPTER

18

STIMULANTS OF C.N.S.—ANALEPTICS

MEDULLARY, SPINAL AND CEREBRAL STIMULANTS AND CONVULSANTS. THEIR PHYSIO-PHARMACOLOGICAL ROLES AND THERAPEUTIC LIMITATIONS

[The analeptics or the restorants, are the stimulants of the medullary, respiratory and V.M. centres but as they also stimulate the other centres of the C.N.S., they are now considered as (a) Cortical, (b) Medullary and (c) Spinal analeptics.

Many drugs like strychnine, picrotoxin, xanthines, camphor and sympathomimetic amines, have been in use for their stimulant actions but at present only a few of them like nikethamide and metrazol are in actual use either in terminal phase of a disease or in depressed conditions of respiratory centre, as in the case of morphia and barbiturate poisonings, for which also, more specific antidotes like nalorphine and megrimide are now available. There is considerable doubt on the efficacy of general analeptics in these conditions. Metrazol is also used for the treatment of schizophrenia along with insulin and electro-shock therapies and also for the screening of antiepileptic drugs.]

A large number of drugs, dispersed in different chapters, stimulate the Central Nervous System at various levels—Cortex, brain stem and cord, often with overlapping of actions. In therapeutic doses, in the normal, their actions are often nil or insignificant but in depressed states of these organs, somewhat better. In higher doses, all of them produce 'Convulsions', the pattern of which differs according to the site of actions. (a) Drugs like dexedrine, ritalin, meratran, caffeine and camphor show predominant psychic stimulation. (b) coramine, picrotoxine, cardiazol and also newer specific drugs like nalorphine and megrimide stimulate medullary respiratory and V.M. Centres and are known as *Analeptics*, in a traditional sense. (c) Strychnine and morphine, stimulate more specifically the spinal centres, though they have other higher actions also.

The term '*Analeptic*' literally means *Stimulants*—in a general sense—cerebral, cardiac, etc., but conventionally, it is taken as to mean, the stimulant of *medullary respiratory*, *V.M.* and *Cardiac Centres*, and restore them to normal conditions, by counteracting the depressed

states of these organs. These objectives are only partially realisable with these drugs and quite often, their uses refer to the psychological acceptance in diseased states and as pharmacological tools in the screening of anticonvulsants and antiepileptic drugs.

CLASSIFICATION

<i>Part of C.N.S.</i>	<i>Stimulants</i>	<i>Depressants</i>
Cortex	Sympathomimetics-amphetamine, Dexedine, Methamphetamine, Dioxyl-paledrine Xanthines-Caffeine, Tropine-atropine, cocaine.	General Anaesthetics Hypnotics Sedatives
Medulla	<i>Direct</i> —Picrotoxin, Coramine, metrazol, camphor, CO ₂ <i>Reflex</i> —Nicotine, lobeline, cyanide. Specific-megimide, nalorphine.	Barbiturates, Morphine, Phethidine, Methadrine. Anaesthetics.
Spinal cord	Strychnine, morphine, codeine, curare.	Myanesin, Meproba- mate & Anaesthetics.

MEDULLARY STIMULANTS

Of the first two groups, only picrotoxin, coramine and metrazol will be studied here. Megimide and nalorphine will be dealt with in the chapters of barbiturates and morphia, respectively.

PICROTOXIN (C₃₀H₃₁O₁₃)

A non-nitrogenous bitter principle, obtained from the seeds of fiah-berries, the climbing shrub growing in South India and Malabar hills. The active principle, *picrotoxin*, is available for injection as 0.3% solution. It is well absorbed from the oral and parenteral routes with an initial delay in the onset of action by 15 minutes and also a short duration of action.

Actions. (a) In animals, it produces clonic, symmetrical convulsions, which do not disappear after the destruction of brain and the cord. (b) In normal subjects, it has little effect on respiration before the onset of convulsions. In patients with depressed respiration, it effectively increases the rate and depth of respiration (Plate-XVIII; Fig. 50.).

(c) Slight rise in B.P. due to stimulation of V.M. centre. During convulsions, rise in B.P. with reflex bradycardia.

Use. (a) To combat respiratory depression in narcotic poisoning like barbiturates. *Dose:* 3 mg/5 mts. till increase in respiration or fibrillary muscle twitches. It is a better antidote for barbiturate poisoning than strychnine but due to the danger of toxicity, not much used.

PENTYLENETETRAZOL

A synthetic compound, also known as *leptazol* (G.B.) *cardiazol* (Germany) or *metrazol* (U.S.A.), is available as injection of 10% solution. It is well absorbed from G.I.T. and parenteral routes, but is usually given I.V. Its onset and duration of action are prompt due to rapid destruction by the liver.

Actions. Limited to C.N.S. In deeply depressed patients, it causes a prompt increase in respiration and a rise in B.P. through the stimulation of respiratory and V.M. centres (Plate-XVIII; Fig. 49). Therapeutic dose—Tabs. of 100 mg and Inj. Leptazoli—10% sol.— $\frac{1}{2}$ to 1 ml. S.C. and convulsive dose 3-12 ml. I.V.

Uses. Though this drug has been much used as an analeptic in narcotic poisoning and in shock therapy, in maniac depressive psychosis, schizophrenia and involutional or senile depression with dramatic improvement in properly selected cases, after 5-10 convulsions, at 2-3 days interval, in a dose of 5 ml. I.V.; its use in convulsion therapy has virtually been replaced by electroshock therapy.

NIKETHAMIDE

Commonly known as *Coramine* is a diethyl derivative of nicotinamide. It is available as 25% sol. in ampoules of 1.5 and 5 ml, containing 0.4 and 1.25 G., respectively. Action is quick and prolonged. It is converted in the body to nicotinamide and is then excreted as N-methyl nicotinamide.

Action. It increases respiration, both *reflexly* through the carotid sinus and *directly*, by acting on the centre, but the latter effect is more important. It does not have any significant effect on other systems.

Uses. Extensively used as an emergent respiratory stimulant in terminal phases of acute illnesses and also in narcotic poisoning with mixed results (Plate-XVIII; Fig. 50).

SPINAL CORD STIMULANTS

There are many drugs, which stimulate this area, and spinal reflexes. In high doses they produce spinal type of convulsions, the action extending sometimes to medulla also. Traditionally, they have been widely used as tonics and analeptics, but their real efficacy has not been substantiated by controlled therapeutic trials. Their dangerous toxicity and side effects have also been deterrent for their successful clinical application. They can, however, be used as pharmacological tools for the screening of depressants of the cord.

STRYCHNOS NUX VOMICA

Also known as '*Kutchila*', (Plate-XVII; Fig. 44) growing in India and Indo-China. It is not a *vomiting nut*, as its name implies. The seeds are disc shaped, ashgrey, bitter, containing—two alkaloids.

Strychnine—0.2—0.5%—Pharmacologically active.

Brucine—0.5—1%—very little active.

Strychnine has a complicated formula— $C_{21}H_{22}O_2N_2$

Preparations

Tinc. nux vomica—0.6—2 ml.

Strychnine HCl—2-8 mg.

Liq. strych. HCl 1% (3-12 m. or 0.2—0.8 ml.)

Metabolism. (a) Quick absorption from the G.I. tract and site of inj. but not through unbroken skin. (b) Short stay in blood—destruction in liver, only 20% excreted through urine, complete in 10 hrs. (c) On repetition of dose, sensitisation is produced.

Action. The main action of strychnine is on the *spinal cord*, though it has got some effect on the *sensory cortex* and *medulla* also.

Cortex—Stimulation of *special senses*—smell, hearing, touch and vision. In moderately high doses, field of vision is increased.

Medulla—Insignificant stimulation in therapeutic doses but has proved itself to be an effective antidote in *barbiturate poisoning* before the newer drugs were discovered.

Cord—Most important site of action of strychnine. (a) Strychnine

enhances the reflex excitability of the cord and produces "Symmetrical, bilateral, spinal convulsions" even after ablation of cortex and medulla.

(b) This is evidenced by the classical experiment of Claude Bernard about its localisation of action on the cord: (i) Strychnine injected into a ligated limb produces no convulsions. While (ii) injected into lymph sac—typical convulsions on the ligated limb also, is produced.

Mode of Action (a) Strychnine renders nervous tissue *hyper excitable* by: (i) Lowering of threshold of excitability. (ii) By removing the normal inhibitory mechanism of sensory paths over motor neurones, so that all paths become accessible to any single afferent stimulus. (b) According to Nachmansohn—Strychnine inhibits cholinesterase and spares Ach. for continuous stimulation of motor neurones.

Other Effects. Of doubtful nature: (a) Stimulation of C.V.S., skeletal and plain muscles etc. undependable. (b) A bitter stomachic in 10^{-5} dil. but *Nux vomica* preferred.

Toxicity. Always acute and accidental. *LD*—60-90 mg. (a) Stiffness of muscles of face and neck, risus sardonicus, fibrillary twitchings, sense of apprehension, excruciating pain, breaking into cold perspiration. (b) Tonic and clonic convulsions, starting with a characteristic 'cry' and lasting for a few minutes. (c) During attack and also during the interval—'Opisthotonus'—the body resting on occiput and heel. (d) Slightest noise or other stimulus precipitates an attack, after 6-8 hours of which, the patient dies in plain consciousness.

Treatment. (a) Absolute rest in a dark room, protected from all disturbances. (b) Use of chloroform and short acting muscle relaxants. (c) No gastric lavage till the patient is well under the anaesthetic. (d) Effective drug therapy—careful use of a short acting barbiturate—*Amytal* 10% sol. I.V., 0.3-1 gm, till the condition is reverted to normal. Use of centrally acting muscle relaxants, discussed earlier.

Uses. (a) Most of the traditional uses—general & C.V. stimulant, general tonic, aphrodisiac—are the relics of the past. (b) As correctly stated by Clark, "Hardly any patient in the British Empire has been allowed to die without a terminal prick of Strychnine and similarly, in the Continent, without a prick of Coramine." Tradition and wrong usage have a slow death.

CEREBRAL STIMULANTS

These drugs in therapeutic doses, cause wakefulness, talkativeness and increased motor activity, while in toxic doses, produce hallucina-

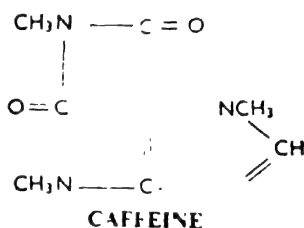
tions, mania, incoordinated movements ending in convulsions, hyperpyrexia and death. Many of the drugs exhibit important pharmacological actions outside the C.N.S. Thus amphetamine and deoxyephedrine are potent sympathomimetics, Xanthines have important effects on heart, kidney and smooth muscle, while atropine and cocaine exhibit parasympathetic blocking and local anæsthetic effects which are their primary actions.

XANTHINES

The Xanthene derivatives—comprise of Caffeine, Theophylline and Theobromine. Their chemical structure is given below:

Of these, Caffeine is preferred for cerebral, C-V and medullary stimulation; Theophylline for coronary dilatation and acute diuresis and Theobromine for prolonged diuresis. These last two will be studied in the Chapter on Diuretics.

CAFFEINE



A purine base, obtained from *Coffea arabica* or *Camellia sinensis*, the percentage content being as follows: (a) Coffea—2%, (b) Tea—4%, (c) Kola—4%, (d) Cocoa—2%.

White, wooly, bitter crystals; sol. 1 in 80, more with sodium benzoate.

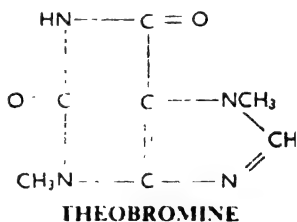
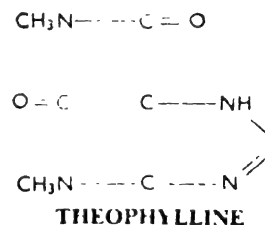
Preparations and Dose

Caffeinae et Sodii Salicylas—

(0.12-0.3 G)

Caffeinae et Sodii Benzoas—

(0.3-1 G)



Illus.—X

Metabolism. Rapid absorption from M.M., S.C. tissues, 80% broken in body as urea and a trace is excreted in urine unchanged or demethylated.

Actions. Legends of coffee beverages and its stimulating action from 5th century onwards. The important actions are as follows: (a) C.N.S.

stimulant—cortex, medulla, heart and respiratory centres. (b) Diuretic. (c) Skeletal muscle.

C.N.S.—In therapeutic doses: The sensory cortex is stimulated resulting in: (a) Increased mental alertness and wakefulness. (b) Increased perception. (c) Increased association of ideas.

All these are demonstrable with ergographic, chronaxy, typing and arithmetical experiments.

With higher doses: (a) Stimulation of motor cortex and convulsions. (b) Medullary—respiratory, vagal and V-M centres are stimulated. These actions are more marked when the centres are depressed.

Muscles: Striated and non-striated, all are stimulated. Latent period of contraction is diminished and its amplitude is increased.

C.V.S. (a) Cardiac rate and amplitude of contraction increased. (b) Central vaso-constriction, peripheral vasodilatation, dilatation of coronary vessels but not of much use in therapy.

Diuresis (a) From dilatation of renal vessels and opening of increased number of glomeruli. (b) From impediment of tubular reabsorption. The net result is *diuresis*.

Chronic Toxicity

(a) Insomnia, nervousness, irritability and palpitation. (b) G.I. irritation and loss of weight.

Uses. Faintings—a cup of hot black coffee. Headache and Migraine—A.P.C. powder.

CAMPHOR

Natural Camphor, obtained from *Cinamomum camphora*, growing in Borneo and Japan. Synthetic Camphor—is a derivative of terpene. Transparent, crystalline, volatile masses; bitter, pungent, imparting cold sensation on the tongue. Solubility—1:700; Alcohol—1 in 1.

Preparations. (a) Aqua camphorae—(0.1%)—1-2 ml. (b) Linimentum camphorae—20%. (c) Spt. camphorae—(10%)—0.3-2 ml. (d) Injection camphorae (1 in 10)— $\frac{1}{2}$ —2 ml.

Metabolism. Quickly absorbed, oxidised to camphoral by liver and excreted in urine-conjugated as glycuronic acid.

Action and Uses

A. Externally — rubifacient and counterirritant.

- B. Internally — C.N.S.** Very little effect in therapeutic doses.
In higher doses epileptiform convulsions.
Hardly any stimulant action on C.V. & Respiratory Systems
but some carminative action.

DEXEDRINE

(a) Dextro-rotatory form of amphetamine, already studied in the chapter of sympathomimetic amines. It is a stable compound—partly oxidised and partly excreted in urine, in unchanged form. It produces marked stimulation of cerebral cortex and possesses less side effects than amphetamine. It produces euphoria and diminished acuity of sensory taste, appetite and hunger. (b) The drug acts by inhibiting amine oxidase resulting in the formation of aldehydes, which is a depressant for tissue respiration. In this manner, stimulating action of the drug on the cerebral cortex is produced. (c) Besides, its use as a *central stimulant*, it is also used in cases of *obesity*—5 mg. t.d.s.

Clinical Applications

Narcotic poisoning. A condition resulting from overdosage of narcotics—a group of drugs which produce irregularly descending depression of C.N.S. and have got a tendency to produce drug habit on prolonged use. The most common agents responsible for this are Barbiturates and Morphia. The condition is characterised by a progressive depression of respiration, which if untreated, leads to death. Basic principles of treatment are: (a) Gastric lavage. (b) Supporting of circulation—25-50 mg. Ephedrine S.C. (c) Combatting respiratory depression by: (i) Oxygen inhalation (ii) Artificial respiration (iii) Analeptics like Metrazol or Coramine.

Metrazol. 0.5 ml of a 10% sol. I.V., every minute till patient responds to stimuli. **Coramine**—5-10 ml of 25% solution I.V. followed by 5 ml every 5 mts, till patient responds to stimuli. Results, on the whole, disappointing.

Megimide and Nalorphine. Specific antidotes to barbiturate and morphine poisoning, respectively, discussed in their respective chapters.

Shock Therapy. Developed for the treatment of mentally disturbed patients, particularly maniac depressive psychosis, schizophrenia and involutional or senile depression. The basic principle is to induce convulsions by:

(a) **Drugs**—like Metrazol.

(b) **Insulin**—in doses sufficient to produce hypoglycemic coma and

convulsions. It is induced daily for not longer than three months. As the therapy is expensive, hazardous and requires skill and experience, it is not much used these days.

(c) *Electro-shock therapy*—has superseded chemically induced convulsions. Treatment of choice for cases of involutional psychotic depressive reactions. It is useful in reducing the time period required to tranquillise over-active and agitated patients. The exact mechanism of its action is however obscure.

With the help of a special electro-convulsimeter, fits lasting for less than a minute, are induced three times a week with a total not exceeding 20 fits. In cases of relapse, the treatment may be repeated.

CHAPTER

19

PHARMACOLOGY OF ANAESTHETICS

TWO TYPES: (a) GENERAL AND (b) LOCAL ANAESTHETICS. ADJUVANTS TO GENERAL ANAESTHETICS. REFRIGERATION ANAESTHESIA. THEIR MERITS, DEMERITS AND CLINICAL STATUS.

[The general anaesthetics, which comprise of three groups of drugs (a) *Volatile liquids*, (b) *Gases* and (c) *Solid* anaesthetics, produce the important actions of loss of all sensations, unconsciousness and muscular relaxation. They have been of immense value not only for modern surgical interventions, but also for the treatment of certain conditions.

Amongst the time old anaesthetics, *ether* still finds its use as an anaesthetic agent but the use of *chloroform* has almost been given up because of its cardio-hepatic toxicity. The newer compounds like *halothane* and the gas anaesthetic *cyclopropane* are of value in surgical anaesthesia and still newer drugs like *thiopental Na* and the steroid compound *viadril*, are finding uses quite frequently these days.

Most of these anaesthetic agents are of potential toxicity and therefore the present practice is to use adjuvants to general anaesthetics in the form of *basal anaesthesia* with tribromethanols or paraldehyde, *preanaesthetic medication* with morphine atropine, scopolamine or pentobarbitone, with induction of more complete muscular relaxation with the peripherally acting *muscle relaxants*.

Modern concepts of anaesthetic procedures are now based on the induction of *balanced anaesthesia* by using two or more anaesthetic agents simultaneously for producing anaesthesia, with lower toxicity and greater safety by any of standard methods of *inhalation* or *injection anaesthesia* and also use *refrigeration anaesthesia* for brain and C. V. operations so that greater viability of tissues even under anaemic conditions becomes possible.]

A fascinating chapter comprising of (a) General anaesthetics and their adjuvants and (b) Local anaesthetics, which, along with antiseptics and antiinfective drugs, have completely revolutionised the scope of modern surgery and laid the foundation for advancements in all branches of surgery, hardly imaginable even a few decades ago.

GENERAL ANAESTHETICS

These are a group of drugs (a) *Volatile liquids*, (b) *Gases* and (c) *Solids*, of diverse chemical nature which possess the unique properties of

(a) Suppression of all feelings and sensations temporarily, (b) Obliterating of consciousness and motor activities while sparing the autonomic functions and (c) Production of muscular relaxation making surgical intervention much easier. All these essential prerequisites, along with minimum toxicity and wider safety margin, are necessary before any particular anaesthetic could be considered to be satisfactory for clinical uses.

Historical. Pain has been the greatest *archenemy* for surgical advancement from the earliest days. The search for the discovery of anaesthesia is, therefore, lost in antiquity: (a) The Egyptians and the Chinese used narcotics and the Indians fermented liquors, for the induction of anaesthesia. (b) Strangulation, cerebral concussion, opium, mandagora (belladonna)—all have been tried by turns up to the time of 'Ambroise Pare' and Simmel Weisse, in the 18th century and even thereafter till:

(i) Nitrous oxide, discovered by Priestley in 1776, was brought into therapeutic use by Wells in 1845.

(ii) Ether, discovered by Valerius Cordus in 1540, was used as an anaesthetic by Morton in 1846.

(iii) Chloroform, discovered in 1831 and introduced as a general anaesthetic by Fluorens and Simpson in 1847.

A violent opposition was launched against Simpson by the ecclesiastic school for veiling the soul of patients with chloroform which was tactfully silenced by him, reminding the Church about the Biblical story of the origin of 'Eve' from the ribs of 'Adam' by God, surely with the help of an anaesthetic. He was then asked to conduct the delivery of Queen Victoria, which he did successfully, by inducing 'twilight sleep' with chloroform and was soon knighted by her, in appreciation of this service.

(iv) After this, more than 9 barren decades passed and then 'ethylene' was discovered by Luckhardt in 1922; *divinyl ether*—by Leake in 1930; and *cyclopropane* by Lukas & Henderson in 1929. The search still ceaselessly continues for the discovery of an ideal anaesthetic, which is yet to be found.

CLASSIFICATION

VOLATILE LIQUIDS	Chloroform, ether, divinyl ether, ethyl chloride, halothane, trichlorethylene, methoxyflurane
GASES	Nitrous oxide, ethylene, acetylene & cyclopropane
NON-VOLATILE ANAESTHETICS	Thiopentone, hexobarbitone, kemithal, viadril

In addition, there are a number of other drugs which are used for:

(a) *Basal Anaesthesia*—tribromethanol (avertin), paraldehyde, chloral hydrate, barbiturates like hexobarbitone, thiopentone sodium and pentobarbital sodium.

(b) *Pre-anaesthetic medication*—morphine, omnopon, pethidine, hyoscine hydrobromide, atropine, phenothiazine derivatives like chlorpromazine, triflupromazine, promazine and barbiturates.

(c) *Muscle relaxants*, referred to earlier.

Chloralose, chloretone and urethane are not used in human but animal anaesthesia only.

In actual practice, there are two types of anaesthesia in use:

(a) *Inhalation anaesthesia*—volatile liquids and gases.

(b) *Intravenous anaesthesia*—non-volatile anaesthetics.

As the alveolar surface represents an area of 70 sq. metres ($80' \times 20'$), and the entire quantity of blood passes through it every 30 seconds, the absorption and excretion of volatile anaesthetics is extremely rapid. This is why the first two groups of anaesthetics became very popular in the beginning. Of late, Injection anaesthesia is more often being used.

General Properties. (a) The general anaesthetics are universal depressants of protoplasm and tissues. It is a reversible process, the nerve tissue loses conductivity and the muscle contractibility. (b) There is elective action on the lipoids of C.N.S. causing an irregularly descending paralysis of cortex → basal ganglia → cerebellum → cord (first sensory & then motor functions)—and lastly medulla. Highly developed functions are affected first.

Metabolism

(a) The *absorption* is proportional to the concentration of the anaesthesia and the pulmonary ventilation. During induction, arterial blood is richer in anaesthetic concentration and during recovery venous blood more so.

(b) Their *fixation* is shorter in brain, longer in heart and longest in adipose tissues.















(c) The *excretion* takes place mostly through lungs in cases of inhalation anaesthetics and through urine, in cases of solid anaesthetics.

Stages of Anaesthesia. There are actually four implicating cortex, spinal cord and medulla.

The *cortical phase* may be divided into: (a) First stage or the Stage of Induction, (b) Stage of excitement and delirium—starting from the

onset of unconsciousness and extending to the onset of surgical anaesthesia.

I. *Stage of Induction or First Stage (a)* Suffocation and holding of breath, coughing. *(b)* Flushed face, pupil dilating, pulse and B.P. increased; struggling. *(c)* Respiration—rapid and irregular, *(d)* All reflexes—superficial and deep—intact.

Stages of Anaesthesia	Respiration Abdom. Thoracic	Size of Pupil	Eye ball movement	Disappearance of Reflexes	Pulse	B P.	Operations
Stage I (Analgesia)			Voluntary	All intact	Fast	Elevated	1st. stage of labour
Stage II (Delirium)			Roving	All intact	Fast	Elevated	Nil
Stage III Plane 1			Sluggish	Conjunctival	Normal	Normal	Thyroid, mastoid, Brain, Thoracic Bladder Caesarean section
Stage III Plane 2			Fixed	Cutaneous Pharyngeal Peritoneal	Normal	Normal	Routine eye and ENT, joint, Abdominal Surgery Urethra, hernia
Stage III Plane 3			Fixed and converged	Corneal	Fast	Falling	Rectal Surgery internal podalic version
Stage III Plane 4				all absent	Thready	Falling	Nil
Stage IV			—	all absent	absent	Shock level	Autopsy

Illus.—XI. Stages of anaesthesia

II. *Stage of excitement and delirium:* *(a)* Blurred consciousness, emotivity and excitement, *(b)* Closed eyes, set jaws, irregular breathing, roving eyeball, dilated but active pupils. *(c)* Analgesia but all the reflexes are intact.

A big whip of *chloroform* may increase concentration in the coronary artery and *adrenaline* secretion, inducing sudden *ventricular fibrillation*—a catastrophic complication. The sensory synapses are paralysed but the motor components of the reflex arcs, are not sufficiently paralysed for favouring muscular relaxation and surgical operations.

III. *Spinal or Stage of surgical anaesthesia:* *(a)* There is tranquillity and unconsciousness; slow, abdominal breathing and slow pulse. *(b)* the pupils are contracted, converged and the eyeball fixed *(c)* Relaxed muscles, and death like mask on facial expression. *(d)* Progressive fall of temperature; to keep patient warm; may otherwise provoke post-operative pneumonia.

IV. *Fourth or Stage of bulbar paralysis:* The warning signals are: *(a)* Deep unconsciousness, dilated and inactive pupil, thready and

unreadable pulse and B.P. (b) Pale, cold, clammy skin, loss of sphincter control, arrest of respiration and heart. Absolute death in 1-4 mins.

Recovery. This usually occurs in the inverse ratio of the duration of anaesthesia. With the cessation of administration, the percentage is reduced almost half in the body. The respiration becomes quiet, stertorous. The reflexes reappear in the opposite order of disappearance. The patient may bring out his secrets at this stage, after which, he passes into a prolonged natural sleep.

Theories of Narcosis. Still insufficiently established.

1. *Lipid theory* of Meyer and Overton (1901). It had taken into consideration the lipid solubility of volatile liquids as against water. Sol. in Fat

Sol. in H_2O . This is known as partition coefficient. The higher the coefficient, the greater is the anaesthetic potency. This does not explain the anaesthetic effects of solids and alkaloids and the theory is not fully tenable.

2. *Surface tension or adsorption theory* of Traube, Lillie and Warburg (1904-1930). According to this, the potency of an anaesthetic should run parallel with its capacity for lowering the surface tension. This accounts for accumulation of drug on the surfaces. This interferes with metabolic rate of cell but does not explain the depressing effect.

3. *Ferguson's theory* (1929). The anaesthetic dose is inversely proportional to the water solubility. Anaesthetic potency depends upon the thermodynamic activity, which denotes the number of molecules of the substance, which in the body after distribution in the different phases, remain free to exert their specific narcotic effect.

4. *Cell permeability theory* of Hoeber, Lillie, Loewe and Winterstein (1907-26). In this it is suggested that increased in cell permeability during anaesthesia, would interfere with the tonic movements necessary for membrane depolarisation. Chloroform, ether and urethane physically limit membrane permeability and prevent depolarisation.

5. *Biochemical theories* (i) Inhibition of Oxidation—(Theory of Quastel, 1952). The respiration of nerve cells is depressed and oxidation of glucose, lactose and pyruvate by brain cells, is inhibited. This reversible process is produced by anaesthetics and alcohol. (ii) Flavoprotein enzyme in brain is highly sensitive to anaesthetics which acts as hydrogen carrier in tissue respiration, between pyruvic dehydrogenase and cytochrome oxidase. (iii) Certain anaesthetics like barbiturates

diminish the production of A.T.P. and ACh. and thus neuronal transmission is blocked, as for the formation of ACh, active acetate is needed.

6. *Neurophysiological or Electrical Theory*—Anaesthesia is accompanied with decreased negative potential of cortex and lessened conductivity through the cerebro-spinal axis and the decreased synaptic transmission (chloroform, ether, ethane or pentobarbitone). It has also been postulated by Magouin (1961) that anaesthetics inhibit the ascending reticular formation which is important for the maintenance of wakefulness.

7. *Newer Physical Theories*—These correlate the anaesthetic potency to the thermodynamic activity or molecular size of the agent. Increased activity has been associated with the magnitude of Vander-Waals correlation factors, referring to molecular volume and attraction. According to Pauling (1961)—hydrated microcrystal formation in C.N.S., and according to Miller (1961), orientation of H_2O molecules around the anaesthetic agents, would account for the anaesthetic proportion of drugs.

In conclusion, no single theory is good enough for explaining the intricate mechanism of anaesthetic action from diverse chemical substances.

(a) Meyer-Overton's Theory gives some indication about partition coefficient and relative distribution of the anaesthetic agents, explaining their action in certain cases.

(b) The biochemical changes observed in the C.N.S. after use of anaesthesia, the oxidative phosphorylation processes, changes in enzyme system, temporary depression of metabolism and tissue respiration, etc. are an index of another set of mechanism.

(c) The potential changes in C.N.S. point out lessened conductivity in the C.S. axis.

All these are indicative of diverse patterns of action but the mechanism of the complete action is yet to be known.

In the very same manner, the SAR of the volatile organic liquids, comprising of diverse groups—saturated aliphatic, ethylene, acetylene, cyclic, halogenated hydrocarbons, do not show much relationship excepting that their potencies and toxicities increase in the homologous series and with the lengthening of the hydrocarbon chain.

Accidents. These may occur during or after the administration of anaesthesia and are the following:

(a) **Circulatory**—hypertension, hypotension and ventricular fibrillation.

(b) **Respiratory**—arrest, breathholding, laryngeal spasm, swallowing of tongue, post-operative aspiration pneumonia.

- (c) Miscellaneous—Ether convulsions; sudden death in status lymphaticus; anaesthetic explosion from inflammable substances, ether, ethylene, etc.

For preventing some of these untoward accidents and for making induction smooth and anaesthesia safe, preanaesthetic medication and use of basal anaesthesia are advocated. This along with muscle relaxants as adjuvants to general anaesthetics, will be separately discussed at the end.

An *ideal anaesthetic*—must satisfy at least 3 persons in the following way:

- (a) The patient—primary concern—comfortable and cheap anaesthesia.
- (b) The Surgeon—Complete muscle relaxation.
- (c) The Anaesthetist—Wide margin of safety and simple technique of use.

At present we have hardly any with these attributes. In future, some unknown gases or solid anaesthetic or a continued use of several devices, would fulfil these conditions.

VOLATILE ANAESTHETICS

Though there are several members of this group possessing general anaesthetic properties, only a few are in actual use and will be briefly studied here.

CHLOROFORM

CHCl_3 , Trichloromethane, belonging to the series of aliphatic halogenated hydrocarbon, is a clear, colourless, highly refractive liquid of sweetish odour, containing 1% alcohol and stored in amber coloured bottle, away from light, to prevent the formation of toxic phosgene. Sp. Gr.—1.47. B.P. 62°C ; Sol. 1 in 200. Dose 1-5 mg.

Preparation: Aqua chloroformi—15-30 ml.—Carminative, flavouring agent and vehicle

Spirit Chloroformi—0.3-2 ml for other purposes.

Actions :

Externally—Antiseptic and cleansing agent.

Internally—Stomachic, carminative and imparts sensation of warmth on taking.

All these actions have limited value and the most important use of the drug is as a general anaesthetic, discussed hereafter.

Anaesthetic effect: Chloroform is one of the most potent, self-sufficient anaesthetic with quick induction, rapid action and complete

Plate XIX

ACTION OF CHLOROFORM AND ETHER

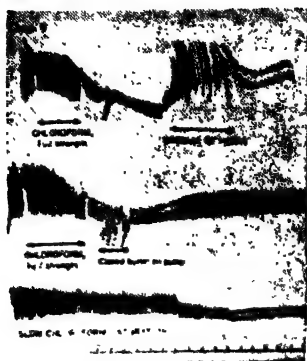


FIG. 51. *Dog ventriculogram* : effects of different concentrations of chloroform on myocardial contractility.

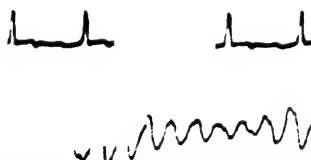


FIG. 52. *Adrenaline chloroform syncope* : normal electrocardiogram (upper panel). Ventricular flutter and fibrillation have occurred after chloroform and adrenaline (lower panel).



FIG. 53. *Ether*

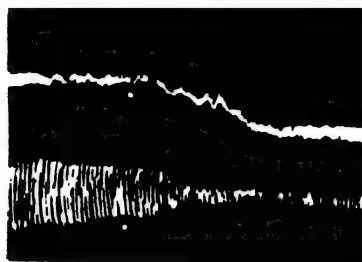


FIG. 54. *Chloroform*

Effect on myocardial contractions and blood pressure. Note the lack of depressant effect of ether.

muscular relaxation. It is thus a 100% anaesthetic with no negligible toxic effect.

The systemic effects of the drug, like those of most other general anaesthetics, refer to the respiratory, C. V., G. I., metabolic, urinary tract, liver and other systems of the body. Briefly speaking, these are as follows:

Respiration. An irritant and depressant, respiration is irregular to start with, slow and deep, shallow and irregular—*cheyne-stokes* type at the terminal stage. (Plate—XIX).

C.V. System. Central and peripheral depression and also depression of myocardium. (Plate—XIX) '*Chloroform-adrenaline syncope*'—occurring as under:

- (i) Inhalation, leading to breath holding—followed by deeper breathing, carrying greater quantity of CHCl_3 to the left auricle and producing poisoning effect.
- (ii) Irritation of the upper respiratory tract setting in '*trigeminocardiac reflex*' from brain stem→cord→stellate ganglion→adrenaline secretion and cardiac acceleration.
- (iii) Simultaneous direct vagal stimulation by chloroform and cardiac slowing.
- (iv) These opposing effects lead to ventricular fibrillation.

Electro-Cardiograph. Multiple foci of ventricular tachycardia with extrasystoles in 50% of cases (Hill, 1932). This disappears on deepening anaesthesia.

G. I. Tract: Irritation followed by depression of tone. Also post anaesthetic vomiting.

Uterus: Little effect on uterine contraction but passes readily through placenta. Due to rapidity of effect it can be used during intervals of pain to induce "*Twilight sleep*".

Action on metabolism: (a) Acidosis. (b) Hyperglycaemia; contra-indicated in diabetes.

Liver and kidney damage: All halogenated hydrocarbons are hepatotoxic drugs producing: (a) acute fatty infiltration and fatty degeneration (b) acute yellow atrophy of liver with characteristic symptoms of vomiting, jaundice, etc. (c) delayed CHCl_3 poisoning sometimes after 1-4 days.

Kidney damage: depressed kidney functions. Proteinuria, in 30% cases, acetone in urine and suppression of urine.

For induction, CHCl_3 is usually used at a conc. of 2% and Ether 5-10% and thereafter they are reduced to 0.5% and 3-5%, respectively.

Uses. Nonanaesthetic uses of chloroform are quite limited and as an anaesthetic agent, due to its toxicity, its use in becoming restric-

RELATIVE CONCENTRATIONS

<i>Type of anaesthesia</i>	<i>% vol. in inspired air</i>		<i>Blood conc. mgm%</i>	
	<i>Chloroform</i>	<i>Ether</i>	<i>Chloroform</i>	<i>Ether</i>
Light anaesthesia	0.25	3	10	100
Deep anaesthesia	0.50	5	15	120
Respiratory arrest	2.00	10	20	180

ted. The mode of administration may be one of the following, for which, elaborate 'anaesthesia apparatus' is available for hospital use.

- (1) Open method—through a mask, by drops.
- (2) Semi-open method with an intervening valve between reservoir and patient, permitting the inhalation of fresh air with each breath.
- (3) Closed method: exhaled carbon dioxide being absorbed by chemical substance like slaked lime.
- (4) Semi-closed method: permitting partial rebreathing.

ETHER

$(C_2H_5)_2O$ is obtained by distilling ethyl alcohol with H_2SO_4 . Very volatile, inflammable, sweet and burning. B.P.— $36^\circ C$ Sol. 1 in 8.5. Impurities—peroxides.

Preparations: (a) Ether Anaestheticus, (b) Spt. Etheris- 1-4ml. (c) Spt. aetheris Co. 1-2 ml.

Actions: *Externally*—due to its rapid evaporation, it acts as a mild anaesthetic, antiseptic, and cleansing agent.

Internally—Carminative, antispasmodic, Hoffmann's anodyne for colic pain and hiccup.

Anaesthetic effect: (a) A potent and dependable anaesthetic with longer induction, less toxicity and weaker muscular relaxation than chloroform. (b) It increases secretions and premedication with atropine is desirable. (c) Anaesthesia may be continued for a longer period than chloroform, as it has a wider safety margin.

Respiration. It is an irritant but not a depressant. It is contra-indicated in pulmonary diseases. It causes quicker and shallower respiration than chloroform.

C.V.S. Flushing of face from cutaneous vasodilation. Chloroform is about 20-30 times more toxic to heart than ether. It may cause auricular but not ventricular extrasystoles. It does not sensitise heart to epinephrine like chloroform.

G. I. Tract. (a) Irritation of m.m. (b) Increased secretion, (c) Post-operative vomitings, in 57% cases. (d) Intestinal tone is inhibited.

Other Effects. (a) Less toxic effects on kidneys and liver. (b) Due to slower effect, labour pain cannot be easily controlled. (c) Partly oxidised and 90% exhaled. (d) Ether convulsion—though rare, may sometimes occur.

Uses. Besides general anaesthesia, it is a carminative, cleansing agent, cardiac stimulant and an anticolic drug.

CHLOROFORM AND ETHER COMPARED

<i>Actions</i>	<i>Chloroform</i>	<i>Ether</i>
Anaesthetic power	greater	lesser
Induction & stages	quick	relatively slow
Muscular relaxation	complete	less complete
Initial excitement	less	more
Secretion, vomiting & hangover symptoms	less	more
C. V. depression	more	less
Toxicity	liver, heart and kidney	Parenchymatous organs
Safety margin	less	more
Contra-indications	liver, heart, kidney, diseases — diabetes, anaemia and acidosis.	Extremes of age, hypertension, aneurysm, pulmonary diseases and thermocautery.

Both Chloroform and Ether have ranked very high as general anaesthetics for over a century and it is only recently that other newer anaesthetics, adjuvants and substitutes have come into the field of operations. These two old members are potent and complete anaesthetics carrying the patients to depths of anaesthesia required. Chloroform has the advantage of quick induction and more complete muscular relaxation, whereas ether is safer and can be used for prolonged anaesthesia. It potentiates the action of muscle relaxants. That Chloroform is much more toxic than ether is shown from *Miller's "Incidence of mortality"*—1 in 2600 for *chloroform* and 1 in 8000 for *ether*. The use of chloroform therefore, as an anaesthetic agent, has practically been discarded even in Scotland, where, due to the discovery of chloroform by Simpson, the popular teaching even a few decades ago, used to be that "Chloroform depresses but sustains the heart, while ether stimulates but exhausts it". This view is shared by none, these days.

DIVINYL ETHER

$(\text{CH}_2:\text{CH})_2\cdot\text{O}$, patented as '*Vinethene*', was introduced by Leake & Chen (1930). It is more volatile than ether; B.P. 28°C . It decomposes readily and is preserved with 3.5% alcohol and 0.01% phenyl naphthylamine.

Special features: (a) It resembles ether but is 7 times more potent and stages pass too quickly. (b) Induction is smooth, margin of safety wide. (c) It produces complete muscle relaxation in $2\frac{1}{2}$ mins. at 18 mg.% (d) Respiration—rapid and shallow. Eye balls not fixed. Patient may rapidly pass into the 4th stage. (e) Cardiovascular toxicity is insignificant and secretions much less affected.

Uses: (a) Superior to NO_2 and *ethyl chloride* for short anaesthesia and may be combined with ether for induction purposes. (b) It is unsuitable for long anaesthesia. It is inflammable, expensive and gives bad hang-on smell.

ETHYL CHLORIDE

$\text{C}_2\text{H}_5\text{Cl}$ is prepared by heating alcohol with HCl . It is extremely volatile and inflammable. B.P. 12°C and is dispensed in special tubes with pin hole exit and spring cap.

Action: (a) Local application from a distance of 1 foot, freezes tissues and produces local anaesthesia. (b) On inhalation, it produces rapid induction with incomplete muscular relaxation. (c) The blood concentration in anaesthesia is 30-50 mg.% (d) It is cardiotoxic and may produce *ventricular fibrillation* like chloroform.

Uses. In view of incomplete muscular relaxation and cardiac toxicity, it is used only as a local anaesthesia for opening out abscesses sometimes.

"TRICHLOROETHYLENE"

$\text{CHCl}:\text{CCl}_2$, also known as '*Trilene*', is used in *trigeminal neuralgia* for relief of pain due to its elective analgesic action on this nerve. It also relieves migraine, sometimes.

The compound which was studied by us for use during World War II for use in shell shock injuries, revealed the following: (a) It was midway between chloroform and ether in anaesthetic properties. (b) Muscular relaxation was less perfect than with ether and excitement and muscle twitches frequent. (c) Toxic symptoms were shown more on lungs and kidneys than on heart and liver. (d) Its special analgesic value deserved special consideration.

HALOTHANE

2-bromo-2-chloro-1:1:1—trifluoroethane, was introduced by the British School (Suckling & Raventos, 1951-56) and has become a popular anaesthetic. It is supplied in amber bottles, stabilised by .01 % thymol. It is not explosive but reacts with a number of metals and also rubber but not with polyethylene containers. A mixture of 68 % of halothane and 32 % of ether forming an azeotropic stable mixture, is used by some anaesthetists but its definitive advantage has not yet been established.

Action. (a) It is less analgesic and has longer induction than chloroform. About 1 % or more is used for maintaining smooth anaesthesia. (b) It resembles chloroform in many respects including E.C.G. changes. (c) It produces less muscular relaxation and is used with N₂O and N.M. blockades. (d) Respiration is depressed and trachial intubation required and used in asthmatics because of direct bronchodilator effect. (e) C.V. effects are the same as with chloroform and there is depression of sympathetic tone. (f) It causes less liver damage and much less plain muscle and metabolic effects than chloroform.

Status—It is a fairly good anaesthetic causing sufficiently deep anaesthesia. It may be useful in asthmatics and also in bloodless plastic surgery. It is likely to stay till replaced by a better one. Its demerits are poor analgesia, slow induction and recovery and also cost.

METHOXYFLURANE

First discovered by Larsen (1958), it is a colourless liquid of sweetish taste and fruity odour. It is fairly stable, non-inflammable and non-explosive.

Actions (a) It can induce any desired depth of anaesthesia without producing hypoxia but because of side effects, it is used with N₂O, barbiturates and muscle relaxants. Delirium during induction is common. (b) It resembles halothane but the depth of anaesthesia is more and effective concentration is 0.2—0.8 %. (c) Recovery is quiet, analgesia considerable but smell of anaesthesia persists. (d) It causes greater respiratory and circulatory depression, bradycardia and probably less cardiac and hepatic toxicity.

Status. The drug produces sufficient depth of anaesthesia and muscular relaxation. It gives prolonged analgesia even after recovery. The slow onset and recovery however, limit its use.

GAS ANAESTHETICS

Nitrous oxide, ethylenes and cyclopropane are the important members.

Nitrous Oxide (N₂O)

Also known as *laughing gas*, it is prepared by heating ammonium nitrate. It is colourless, sweetish, marketed in cylinders and produces explosion if combined with ethylene.

Anaesthetic effect. (a) Rapid but light anaesthesia, the patient experiences sweetish taste, absence of suffocation, marked exhilaration and confusion. Vivid amorous dreams, particularly in women, sometimes implicating the Doctor medico-legally. A sister should, therefore, always be kept by the side of the doctor, while administering this anaesthetic. (b) The patient becomes unconscious in about 30 seconds and recovers within 2-3 minutes of the cessation of anaesthesia. (c) Anaesthesia is extremely light and even Plane 1 of Stage III is not attainable. (e) It is a safe anaesthetic with a mortality rate of 10^{-6} ; dogs having withstood anaesthesia for 72 hours continuously with impunity.

Anaesthetic effect of different concentrations of N₂O and O₂ mixture.

N₂O 80% + O₂ 20% — blurring of consciousness and analgesia.

N₂O 86% + O₂ 14% — complete analgesia.

N₂O 89% + O₂ 11% — light anaesthesia.

N₂O 94% + O₂ 6% — complete anaesthesia.

Other Effects: (a) Heart and respiration accelerated, (b) B.P. rise, (c) Face cyanotic, (d) Pupils dilated, (e) Muscular twitchings.

Anaesthetic blood concentration is 50 mg.%, whereas asphyxial concentration is 60 mg.%. This difficulty is partially obviated by administration of O₂. The gas has to be supplemented by basal anaesthetics like I.V. barbiturate or intrarectal bromethol.

Ethylene C₂H₄

A highly volatile, colourless gas, prepared by dehydrating alcohol. A 90: 10 mixture with O₂, is used.

Action. (a) Similar to N₂O in action. (b) Induction—rapid, agreeable and without irritation. (c) Anaesthesia—in 2-5 minutes, carrying patients to lower border of Plane 1 of Stage III. (d) Respiration, heart, B.P., bronchial secretion—almost normal. (e) Renal and hepatic functions unimpaired. (f) Recovery—in 2-3 minutes. (g) Post-operative vomiting in 33%, instead of 57%, for ether.

Disadvantages (a) Explosion, (b) Imperfect muscle relaxation.

Uses. On the whole limited. (a) Obstetrical analgesia (b) Encephalography.

Cyclopropane

A simple cyclic hydrocarbon. A colourless gas with characteristic odour. Explosive mixtures may occur with air, O₂ and N₂O in certain concentration.

Anaesthesia. (a) A 100% anaesthetic with the following effective concentrations.

- | | | |
|-------------|-------|-----|
| (i) Plane | I : | 5% |
| (ii) Plane | II : | 20% |
| (iii) Plane | III : | 25% |
| (iv) Plane | IV : | 45% |

(b) Induction rapid and smooth 1-5 mins. and recovery immediately after cessation of administration. (c) Administered by closed circuit method—mixed with varying concentrations of O₂, to avoid wastage, as it is an expensive gas. (d) Effective blood concentration during anaesthesia is 17-28 mg% (e) No irritation of respiratory mucosa, no irregularity or depression of respiration, relaxation of bronchial musculature is produced only with high doses. (f) Not a myocardial depressant like chloroform but may produce reflex arrhythmias. (g) Does not affect liver or kidneys.

Status. (a) Ease of induction and fairly wide safety margin (3 times). (b) Absence of irritation—smooth and regular respiration. (c) Absence of visceral damage. (d) Absence of nausea and vomiting.

Unlike ether, relaxation of abdominal muscles not always complete, for which supplementary ether may be needed. Also risk of ventricular arrhythmia and explosion.

Uses. All types of surgical operations and more particularly: (a) Thoracic surgery. (b) Congestive heart failure. (c) Obstetrical interventions. (d) Exophthalmic goitre operations.

SOLID OR NON-VOLATILE ANAESTHETICS

As already observed, volatile liquids and gases could not be considered to be free from major limitations. From the knowledge of CNS depressants, it was conceived that certain non-volatile substances could

also be used for inducing general anaesthesia. The work was started with *animal anaesthetics*—chloretone, chloralose and urethane, and the concept of human anaesthesia started with the discovery of barbiturates as *injection anaesthesia*.

CLASSIFICATION

<i>Barbiturates</i>	<i>Non-barbiturates</i>
Thiopentone sodium Hexobarbitone sodium Thiobarturate derivatives— kemithal, surital, methitural	Dolitron Steroid derivative—viadril

General Considerations. The merits of this group of anaesthetics are: (a) Pleasant induction without any excitatory stage. (b) Rapidity of action, (c) Depth controllable by adjustment of rate of injection.

The demerits are (a) *Chain reaction* till detoxified and excreted, whereas in cases of inhalation anaesthesia, rapid concentration changes after cessation. (b) Respiratory depression and hypotension. Analeptics and pressor drugs should be kept ready at hand. (c) Insufficient muscle relaxation, necessitating supplementary muscle relaxants or other anaesthetics. (d) Parasympathomimetic action producing laryngo and bronchospasms, requiring prior intubation in certain cases.

PENTOTHAL OR THIOPENTAL SODIUM

A barbiturate, obtained by the condensation of thiourea and malonic acid. It is quickly oxidised and excreted in urine, the rate of oxidation being 1/30/per minute.

Action. (a) Rapid and pleasant induction with fair muscular relaxation. (b) Respiratory and C.V. depression, requiring coramine, megimide and cardiazol for antagonising the effect, if necessary.

Uses. (a) 2-5 ml. of 2.5% sol. freshly made, initially by slow I.V. inj. to start with. Subsequent doses depending on the nature of operation. Total dose not exceeding 1.5 gm. (b) Short operations lasting for 15-20 minutes: (i) Orthopaedic manipulations, (ii) Cystoscopy, (iii) Obstetrical repairs and D and C, (iv) Psychoanalysis.

Pentothal, supplemented with N₂O or cyclopropane, may be used for major operations.

Contraindications (a) Respiratory and cardiac diseases, (b) Children below 10 years. (c) Shock and haemorrhage.

Evipan or Hexobarbitone Sodium

White, crystalline, odourless, hygroscopic, bitter powder. Soluble, but unstable and should be freshly made. Usually 10% sol. is used I.V. at the rate of 1 ml./10 secs. *Initial dose*—3 c.c., repeated after 30 seconds and supplemented by further doses. *Total dose* 14 mg./kg.

Action. (a) Short and inadequately deep anaesthesia with incomplete muscular relaxation and twitchings. Supplementary cyclopropane or N₂O necessary. (b) 'Artificial air way', O₂+CO₂ mixture, and respiratory analeptics are often necessary. (c) Recovery usually quick. Occasionally mild excitement, amnesia and prolonged sleep may be observed.

Uses. (a) Short surgical operations. (b) Removal of painful sutures, orthopaedic manipulations. (c) Pneumoencephalography.

Kemithal. A derivative of thiobarbituric acid, gradually replacing Pentothal sodium for I.V. anaesthesia. Its dosage schedule and mode of administration are the same as for Pentothal. It produces less respiratory depression and laryngeal spasm.

Surital and Methitural. (a) Two newer ultra short acting thiobarbiturates, the former known as *Thioseconal sodium*. (b) They are essentially similar to Pentothal but may raise B.P. and produce higher incidence of dizziness during recovery. (c) 2.5% sol. is used with an initial dose of 3-6 ml. at the rate of 1 ml./5 sec. *Total dose*—not exceeding 40 ml.

Dolitrone or Doriden. Another short acting compound, not belonging to the group of barbiturates, is a white, crystalline powder, insoluble in H₂O, but the Na salt is soluble. It is 1/3rd as toxic as Pentothal with short recovery period and laryngospasm. As the drug produces a high incidence of thrombophlebitis, it is not much used as I.V. anaesthetic.

VIADRIL

From the work of Selye (1941) & Laubach (1955), the depressant effect of some of the *steroid* compounds on the CNS was observed and this was clinically substantiated by Howland *et al* (1956) on patients.

21-hydroxy pregnanedione sodium succinate, also known as *Viadril*, has thus become a promising new addition to I.V. anaesthetics. It is a white, crystalline powder, readily soluble in water, the aqueous solution being alkaline (pH 8.5—9.8). It is used as 2.5% solution, with a total dose not exceeding 40–60 ml. (1–1.5 gm). The injection is given slowly in about 5 minutes. It has a wide therapeutic index and no hormonal effect. It does not produce any visceral damage.

It has analgesic and anaesthetic effect producing sleep, muscular relaxation and depression of reflexes, without depressing the vital functions. E.E.G. changes are very similar to those of barbiturates.

It acts as a potent uncoupler of oxidative phosphorylation, as in the case of pentobarbiturate and produces hypotension, thrombophlebitis and needs supplementary N_2O and O_2 .

ADJUVANTS TO GENERAL ANAESTHETICS

Under the coverage of this old terminology, used in dispensing, meaning, the use of additional drugs for reinforcing the main actions or modifying the side-effects of principal drugs, three distinct groups of drugs, referred earlier—(a) Basal anaesthetics (b) Preanaesthetic medication and (c) Muscle relaxants, are included. Of these, the muscle relaxants have already been discussed in chapter 14. The remaining drugs, not dealt with elsewhere, will be considered here.

BASAL ANAESTHETICS

These are also CNS depressants, producing some degree of unconsciousness and mild anaesthesia and used before the administration of general anaesthetics. They are: (a) Tribromethanol (avertin), (b) Paraldehyde, (c) Chloral hydrate (d) Hexobarbitone (e) Thiopentone, and (f) Pentobarbital.

They not only quieten nervous patients prior to the use of other anaesthetics but also produce: (a) Smooth induction (b) Synergistic action, reducing dosage schedule and toxicity of the main anaesthetic, the patient remaining under, for a specified period.

Tribromethanol

Also known as *avertin*, it is a white crystalline powder and chemically related to chloral hydrate and ethyl alcohol. There are two ethanol—tribromo and trichloro, both endowed with anaesthetic properties.

Tribromethanol is very little soluble in water and is therefore made

soluble in amylene hydrate at a concentration of 1:1 as stock solution. For rectal use—2.5 ml. in 100 ml. (1:40) of distilled water,

Action. (a) Used intrarectally $\frac{1}{2}$ hour before operation, it acts as a basal anaesthetic to be supplemented by N_2O , ether or cyclopropane, for producing complete anaesthesia. Its average dose is 6-8 ml. for females and 9-10 ml. for males.

Fifty percent of the solution is absorbed in 10 minutes and 95% of the rest in $\frac{1}{2}$ an hour. A concentration of 5 mgm. % in blood, produces mild narcosis, while 8 mg. % produces deep narcosis. A dose of 80 mg./kg. produces basal anaesthesia for 2 hours. The drug is conjugated in the liver with glycuronic acid and excreted in urine—about 80%, in 48 hours. It is a powerful depressant of CNS, as well as respiratory centre, blood pressure, myocardium and liver.

Uses. Only as a basal anaesthetic in: (a) Brain surgery needing postanaesthetic sedation, (b) Thyrotoxicotic patients, (c) Biopsy procedure.

Contraindications: (a) Alcoholics, (b) Cardiac, renal and hepatic patients.

BARBITURATES

The ultra short acting compounds, in lesser doses, are specially used as basal anaesthetics in cases of children and thyrotoxicotic patients.

Pentothal. (a) 2.5% sol. in 150-300 mg. dose, I.V. is sufficient. (b) In children 10% solution, 1 gm./50 lbs. of body wt./rectum.

Hexobarbitone. (a) 10% solution 200-400 mg. I.V. (b) In children 40 mg./kg. can be given per rectum. **Thiamytal.** 2.5% sol. I.V., in a dose of 100-300 mg.

Paraldehyde

Besides its hypnotic use, the drug has long been used per rectum, for producing basal anaesthesia. A retention enema of 15-30 ml. as 10% sol. in H_2O ; *Adult dose*—not exceeding 30 ml. Though very safe, it is not liked by patients, because of bad odour during pulmonary excretion.

PREANAESTHETIC MEDICATION

It is designed to give more comfort to the patient while enhancing the efficiency of anaesthesia—by lessening apprehension and resistance of the patients, untoward side-effects and also dose and toxicity of the main anaesthetic agents. Drugs used are a combination of narcotics or sedatives with an anti-secretory agent—as detailed below: (a) Morphine, (b) Omnopon, (c) Pethidine, (d) Hyoscine HBr, (e) Atropine, (f) Phenothiazine derivatives—chlorpromazine, trifluoromethazine and promazine, (g) Barbiturates.

Morphine. One of the most widely used drugs. A tranquillising, sedative and analgesic agent making induction smooth. Dose—10-15 mg/SC/; 1-1½ hr. before operation.

It may however, cause (i) Respiratory depression, (ii) Postoperative constipation, (iii) Retention of urine, (iv) Interference with pupillary signs.

Meperidine or Pethidine, a morphine substitute, which combined with Scopolamine, is used for obstetrical analgesia. Dose—50-100 mg. I.M., 45-90 mts. before anaesthesia. It does not interfere with pupillary reflexes. Besides its analgesic action, it relieves spasm of smooth muscle which is a special advantage in abdominal surgery.

Atropine. (a) In a dose of 0.5 mg. S.C., it diminishes secretions and acts as a mild respiratory stimulant with prevention of broncho and laryngospasms, as well as hiccup. (b) It also prevents postoperative vomiting, pulmonary complications and possibility of cardiac arrhythmias. (c) It however, alters the pupillary signs and in higher doses, may stimulate C.N.S.

Scopolamine. Like atropine, it diminishes secretions and is also a tranquillising agent. Dose—0.3-0.6 mg/S.C. It also produces mydriasis and excitement in certain cases.

Pentobarbital and Secobarbital. In doses of 50-100 mg./OS and 200-300 mgm./OS respectively, these drugs are sometimes used as preanaesthetic medication for quietening the patient.

THERAPEUTIC MEASURES

Modern anaesthetic techniques are based on balanced anaesthesia by mixing of two or more anaesthetic agents in order to achieve advan-

tage in administration, required degree of muscular relaxation, safety and avoidance of deleterious effects on the vital organs by higher concentration. It is thus possible to use lower concentrations of each agent and yet produce accentuation of desirable effects.

Equipment used for inhalation anaesthesia may vary from simple open drop mask to a complicated anaesthetic machine, which delivers measured quantities of anaesthetic gases or vapours of volatile liquids from specially calibrated vaporisers.

Usually, the anaesthesia is induced by injecting a small dose of thiopentone sodium or evipan and then a mixture of nitrous oxide and oxygen or cyclopropane and oxygen, is delivered through a breathing circuit of an anaesthetic machine. Vapours of ether, trichlorethylene, halothane are added to the mixture by incorporating suitable calibrated vaporisers in the circuit. These circuits are non-rebreathing or 'closed' where carbon dioxide is absorbed by means of sodalime. The muscular relaxation is achieved by tubocuramine or succinyl choline chloride by injecting minimal doses of relaxants, intravenously. Controlled ventilation is used in these cases to ventilate the patient adequately so that homocostasis of oxygen and carbondioxide levels in blood and tissues, are maintained.

With the advent of new volatile anaesthetic agents like halothane and methoxyflurane, chloroform has almost disappeared from the modern operation theatres. Ether is still considered to be a safe and very useful anaesthetic and, but for its inflammable nature, it is extensively used as an all-purpose anaesthetic agent for general anaesthesia.

Nonvolatile anaesthetics of the barbiturate series are not only used for anaesthesia but have a wide therapeutic utility. They are very valuable in the treatment of convulsive disorders like status epilepticus, eclampsia and tetanus. Intermittent positive pressure breathing techniques are also extensively used for maintaining controlled ventilation in cases of tetanus, where relaxants are useful to control the spasms. Thiopentone sodium and relaxants are also valuable in electroconvulsive therapy for psychological disorders.

Intravenous anaesthesia has gained universal popularity and soluble thiopentone sodium is used for this purpose. The solutions have been employed in concentrations of 1, 2.5 and 5 per cent. The 2.5 per cent appears to be the concentration of choice amongst most anaesthesiologists. 2 to 5 ml solution (2.5 per cent) are injected slowly in $\frac{1}{2}$ to 1 minute. The induction is almost immediate and the respiration is depressed. The needle is allowed to remain in the vein and intermittent injections are made, depending upon the type of patient and the nature of operation. This technique is not recommended for pro-

longed anaesthesia and doses of 1 to 1.5 gms should not be exceeded. For major surgical procedures, intravenous anaesthesia is combined by cyclopropane or nitrous oxide and oxygen. Better relaxation is achieved by using curare, gallamine or succinylcholine chloride.

The surgical procedures for which intravenous anaesthesia appears to be well suited, are: (1) orthopaedic operations and manipulations, (2) genitourinary procedures, e.g. cystoscopies and transurethral resections, (3) obstetric repair procedures, (4) dilatation and curettage.

REFRIGERATION ANAESTHESIA

A recent development that has very much advanced the scope of cardiac and neuro surgeries, which can now be carried out at low temperature with less loss of blood and greater tissue viability under reduced oxygenation. It can be studied under the following heads:

(a) *Refrigeration analgesia* is the application of cold to a localised part of the body for blocking local nerve conduction of painful impulses. This can be achieved by (i) Ether or Ethyl chloride spray—if the surface is smooth, causing localised freezing and analgesia, (ii) If the whole limb is to be cooled, a tourniquet is applied proximal to the part to be cooled, for avoiding undesirable chilling of other parts and the part then enclosed in ice for $\frac{1}{2}$ —3 hrs. Afterwards the part is dried before operation. It is *useful* for amputation of limbs in cases of arteriosclerotic or diabetic gangrene and has the *advantages* of (1) Absence of shock, (2) Absence of postoperative pain.

(b) *Induced hypothermia*. In this case, temperature of the whole body is reduced by application of cold. With the reduction of temperature of the body, the metabolism is lowered and dangers of hypoxia and cellular damage resulting from occlusion of circulation, of brain, heart and liver can be avoided.

Method: After anaesthetising the patient, cooling is accomplished by the following methods: (a) Use of muscle relaxants or lytic cocktail for preventing shivering and for allowing adequate peripheral vasodilatation for facilitating heart exchange, (b) Immersion in cold water (6–10°C), (c) Ice bags, (d) Refrigerated blankets, (e) Air cooling and (f) Extracorporeal cooling by heat exchangers.

The temperature is thus reduced to 30°–28°C and this allows circulatory arrest for 10 minutes. However, in some cases, *ventricular fibrillation*, a serious complication, may result for which, immediate use of *defibrillator* becomes necessary. By *cardiopulmonary bypass* and *heat exchanger* the temperature can be reduced up to 15°C allowing complete circulatory arrest for 50 minutes. It is very useful in newer

surgical procedures. Gradual rendering should be done after the operation.

LYTIC COCKTAIL

Laborit and Hygneuard in 1951, used chlorpromazine and promethazine to potentiate anaesthesia. Subsequently, pethidine was added to the combination and this mixture, known as *Lytic cocktail*, is used to provide: (a) depression of reticular formation and inhibitory effect in all cellular activity, (b) Inhibition of sympathetic activity, (c) Depression of heat regulating centre, (d) Peripheral antagonism to adrenaline and noradrenaline, (e) Depression of the tone of muscles, (f) Prevention of shivering.

CHAPTER

20

PHARMACOLOGY OF LOCAL ANAESTHETICS

GENERAL PROPERTIES, TYPES, MODES OF STUDY AND CLINICAL STATUS

[A number of drugs depresses the *sensory nerve endings*. Some of them like belladonna, camphor, menthol and aconite relieve pains of inflammation and are known as *local anodynes*. Others remove all sensations and cause muscular relaxation, as in general anaesthesia, without producing any hiatus of the consciousness. These are known as *Local anaesthetics* and are being increasingly used for major or minor operative procedures, often in preference sometimes to the use of general anaesthetics.

The local anaesthetics cause '*surface anaesthesia*' on skin and mucous membrane when locally applied and *infiltration* or *terminal anaesthesia* on hypodermic injections in the field of operation. Injections around nerve trunks produce *conduction* or *block anaesthesia* to these part supplied by the nerves and also saddle, nerve root, epidural and caudal types of anaesthesia, depending on whether the anaesthetic is injected into the cerebrospinal fluid, epidural or intervertebral space or into the sacral canal.

Besides the three older members, *cocaine*, *procaine* and *amylocaine*, a number of compounds, allied to each one of them, has also been found out and being used with advantage. Cocaine is no more used for any other form but the surface anaesthesia, these days, due to addiction liabilities.

In actual practice, for *surface anaesthesia*—cocaine, butocaine, orthocaine, benzocaine, and xylocaine ; for *infiltration anaesthesia*—procaine, monocaine and lidocaine and for *spinal anaesthesia*—percarine, stovaine and lidocaine, in association with a pressor agent—ephedrine, mephenteramine, methedrine, neosynphrine and noradrenaline, for counteracting the fall of B. P. in spinal anaesthesia, from the paralysis of the sympathetic tone, are used.

Besides operative uses, some of the local anaesthetics are also used for *therapeutic nerve block* in trigeminal neuralgia, stellate ganglion block in causalgia of upper limb and auriculotemporal syndrome and lumbar sympathetic block in peripheral arterial disease and causalgic states of the lower limb.]

A large number of drugs are capable of depressing sensory nerve endings. They are:

- (a) *Local Anaesthetics*—to be studied hereafter.
- (b) *Anodynes*—Belladonna, camphor, aconite, menthol.
- (c) *Protoplasmic poisons*—Phenol, quinine, CO₂.

The local anaesthetics act electively on the sensory nerve endings, causing temporary loss of all sensations and even motor paralysis.

Plate XX

SITES OF ACTION AND STRUCTURE OF LOCAL ANAESTHETICS

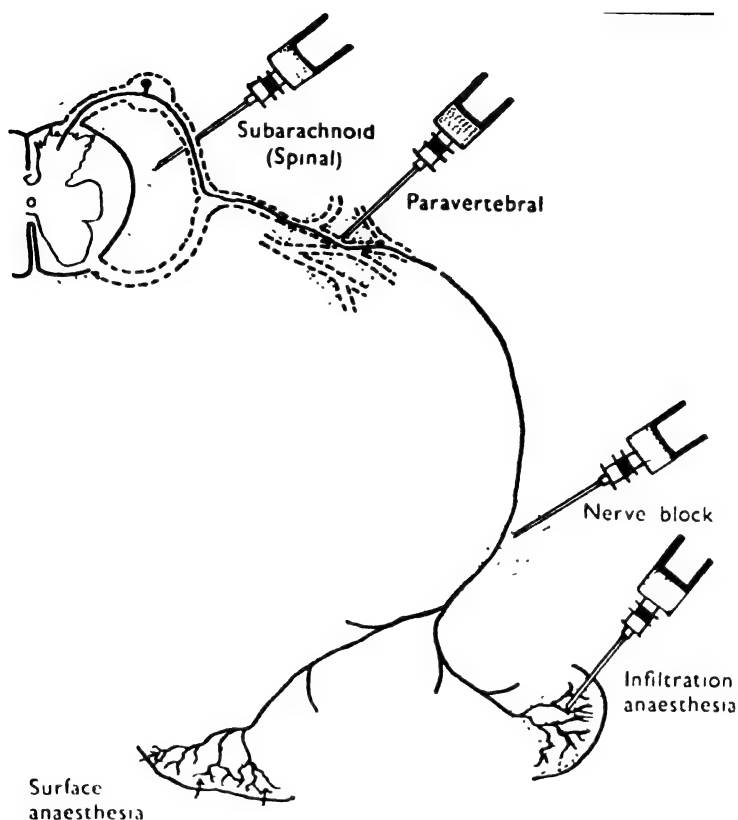
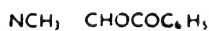
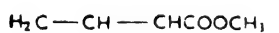
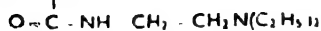
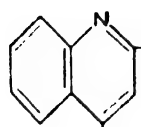


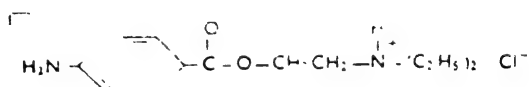
FIG. 55. Sites of sensory pathways used for producing local anaesthesia.



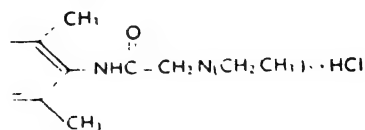
Cocaine



Nupercaine (Dibucaine hydrochloride)



Procaine hydrochloride



Lidocaine (Xylocaine hydrochloride)

The protoplasmic poisons destroy tissue protoplasm and produce more permanent anaesthetic action. The anodynes relieve pain and inflammation when applied locally on the skin.

General Properties. Applied on the motor nerves, impulse transmission; applied on the afferent nerves, reception and transmission of sensory stimuli; and applied on the mixed nerves, first sensory and then motor component, are affected. The effects are temporary, reversible and localised. They do not produce any general anaesthetic action and no unconsciousness.

Further, some of the members produce—C.N.S. stimulation and even convulsions; blockade of myoneural junction and ganglionic synapses; antiarrhythmic action and also spasmolytic action on smooth muscle.

Mode of Action. Not fully established Knowledge of conduction and synaptic transmission of impulses, is not fully known. However, sensory nerve endings, ganglionic synapse, neuromuscular junction, and nerve trunks, are all depressed.

The depression of transmission of impulses in both sensory and motor nerves, the fine, non-medulated nerve fibres being blocked more rapidly. The action on the spike potential is affected and the ionic migration of sodium from outside and potassium from inside, occurs differentially in rising and falling phases of action potential. Stabilisation of potential on the cell surface results in conduction changes. The intracellular action takes place in cationic form of the base and it is enhanced by the alkalisation of the solution. There is elevation of the threshold for excitation of the membrane and also depolarisation, in a manner, analogous to C_{10} , at the myoneural junction.

An ideal local anaesthetic should be (a) Soluble in water and stable on boiling, (b) Its action should be selective, potentiated by adrenaline, free from local irritation and drug habit.

Method of Evaluation. This can be carried out both by animal, as well as, human experiments. The important ones are:

(1) Abolition of the blinking reflex on touching the cornea with a hair aesthesiometer after instillation of the solution of the local anaesthetic agent in the conjunctival sac of rabbit.

(2) Abolition of pain sensation after subcutaneous infiltration of a local anaesthetic agent in guinea pigs.

(3) Study of plexus anaesthesia in *Rana tigrina* after submerging the exposed lumbar plexus with any local anaesthetic solution and

then determining the prolongation or absence of reflex withdrawal of the hind limbs in acid solutions.

Classification. More than one approach.

A. *Chemical-alcohol group*—phenol, menthol, benzyl alcohol.

Ester group—cocaine, benzocaine, procaine. *Misc. group*—xylocaine, nupercaine, quinine and urea. or better still:

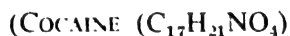
- (1) Natural alkaloid: Cocaine and allied compounds.
- (2) Synthetic compound: Procaine, stovaine, percaïne and allied compounds.

B. *Therapeutic* : (a) Surface anaesthesia, (b) Infiltration anaesthesia, (c) Block anaesthesia, (d) Spinal anaesthesia. Already described (Plate—XX ; Fig. 55).

Mode of Application:

- (a) Local application on the skin and mucous membrane and also by iontophoresis. This is known as 'surface anaesthesia'.
- (b) Hypodermic injection, 'infiltration' or terminal anaesthesia.
- (c) Injection around the nerve trunk, 'conduction or block anaesthesia'.
- (d) Subdural or subarachnoid injections producing saddle, nerve root and epidural types of spinal anaesthesia.

Structure Action Relationship. This is illustrated in (Plate—XX ; Fig. 56) Novocaine is the typical example. (a) Tertiary amino ester of aromatic acid—responsible for local anaesthetic action—effect increasing with the lengthening of the chain. (b) These tertiary amino group increase solubility but the drug acts as base in the tissue.



An alkaloid, obtained from '*Erythroxylon coca*' growing in South America. The leaves contain 0.5% of cocaine, which is a derivative of the base—*ecgonine*, closely related to *tropine* and *atropine*. *Chemically*, it is 'methyl benzoyl ecgonine'.

Colourless, crystalline substance, bitter, followed by tingling and numbness. The base is almost insoluble (1:1300) but the HCl salt is very soluble (1: 0.5). The solution is thermolabile and is to be sterilised by '*Tynadallisation*'. Cocaine comes under narcotic regulation.

Preparations

Cocaine HCl	:	8—15 mg
Solution	:	1—10%
Oculentum	:	0.25%

Metabolism. It is very little absorbed through unbroken skin but more through mucous membrane and s.c. tissue. It is hydrolysed in the G.I. tract, detoxicated in the liver and excreted in urine—partly as ecgonine and partly unchanged.

Action. *Only the local action*—is of therapeutic value, while *systemic action* is mostly of toxicological importance.

Local—Elective action on the sensory nerve endings, producing surface and block anaesthesia.

Systemic—(a) Stimulation of C.N.S., followed by depression. (b) Peripheral sympathomimetic action by inhibiting amine oxidase—(i) Tachycardia, (ii) Vasoconstriction, (iii) Mydriasis, (iv) Exophthalmos.

Other Effects. (i) Cocaine fever, (ii) Stimulation of respiration. (iii) Caffeine like stimulation of muscle. (iv) Diminished gastric secretions and hunger. (v) Motility of gut—increased in small doses and decreased in large doses. (vi) Anaesthetic effect on gut on oral administration.

Toxicity. Worst narcotic but tolerance slightly less than with morphine. Usual LD—200 mg. but death has occurred from less than 60 mg.

Chronic Addiction—from: (a) Chewing, (b) Snuff—perforation of septum, (c) Pricks, the characteristic features being: (i) Poor digestion, emaciation, wrinkled skin, cocaine bugs. (ii) Gross mental changes—loss of memory for dates; introversion, moral depravity, perverted sexual habit. Also insomnia and hallucinations.

Treatment—On the same lines as for alcohol and morphia but prospects of cure are remote.

Uses. Almost discarded, excepting for '*Surface anaesthesia*' of mucous membrane—Ophthalmology and E.N.T. For risk of habit formation, not used for infiltration or any other anaesthesia.

PROCAINE

Also known as *novocaine*, it was synthesised by Einhorn in 1905, with a view to eliminate—(a) Drug habit and (b) Sympathomimetic side effect of cocaine.

It is diethyl amino ethanol p-amino benzoate. The HCl salt is a white crystalline powder; (solubility 1:1), the solution stands autoclaving. It is incompatible with alkalies.

Preparations

- (a) Procaine HCl—Tab. 30-120 mg.
- (b) Inj. Procaine HCl—1-2% for infiltration & block anaesthesia, 5-10% sol. in doses of 50-500 mg. for spinal anaesthesia & 0.1 to 0.2% for I.V. use in cases of burns.

Actions. (a) Fairly similar to cocaine but much less central stimulation, drug habit and no sympathomimetic action. (b) Procaine sulphonamide antagonism—mediated through PABA and is therefore contraindicated in sulphonamide therapy.

Toxicity. 1/4th as toxic as cocaine. Occasional death even with 10 mg. from cardiovascular collapse, due to allergy. Can be controlled by barbiturates.

- Uses:** (a) It is an ideal drug for infiltration but unsuitable for surface anaesthesia due to its poor power of penetration.
- (b) It has been used in delayed serum sickness and urticaria and also in cardiac arrhythmias in doses of 30-70 mg. I.V., but procainamide or pronestyl is preferred.
- (c) In a dose of 4 mg/kg (0.1% solution) I.V. procaine has been used for the relief of pains of burns, arthritis and serum sickness but because of its high degree of toxicity causing sometimes faintness, cyanosis, procaine dermatitis (Surgeon's finger) and even cardiovascular collapse, its use is now limited only to infiltration anaesthesia.

STOVAINE

Also known as *amylocaine*, is benzoyl ethyl dimethyl aminopropanol. It was synthesised by Fournau (1904) and the HCl salt—white stable powder, sufficiently soluble, is used. *Dose.* 20-45 mg. up to 100 mg. intraspinally.

Action. Almost as active as Cocaine, but unsuitable for surface anaesthesia due to irritating sensation of foreign body on the cornea.

The drug is free from psychic stimulation, sympathomimetic action and habit formation. It is more toxic than procaine, but less toxic than cocaine.

Uses. Regional and spinal but not surface anaesthesia.

Besides the above three older local anaesthetics, there are other groups of compounds: (a) Allied to cocaine, (b) Allied to procaine, (c) Allied to stovaine, and (d) Miscellaneous group.

ALLIED TO COCAINE

Tropacocaine. Derived from *Java coca*: (a) It is $\frac{1}{4}$ as toxic as Cocaine. (b) The solution is stable. (c) It does not produce vasoconstriction, nor dilates the pupil, nor stimulates C.N.S. nor produces drug habit. (d) 3% solution is used for surface anaesthesia for ocular application.

B-Eucaine—benzamine lactate, a degradation product of cocaine, stable but weaker, slower in action and less toxic than cocaine. It does not possess other effects of cocaine. *Dose*: 7.5—30 mg.

Uses. (a) Surface anaesthesia—2-10%, (b) Conduction anaesthesia—2.5%.

ALLIED TO PROCAINE

Butyn. or Dibutyl amino propanol, commonly known as *butacaine*, resembling procaine in many respects but is a superior *surface anaesthetic*. Its special features are: (a) Better penetration into tissue than cocaine. (b) Quicker and longer action. (c) No mydriasis nor vasoconstriction. (d) Less damaging to cornea than cocaine.

Uses. (a) Surface anaesthesia for skin and mucous membrane—2% sol. or ointment. (b) Unsuitable for injection anaesthesia.

Pantocaine or Amethocaine: It is 5 times more toxic and 10 times more active than cocaine. It is used for surface, infiltration and spinal anaesthesia, in the following concentrations:

- (a) For surface anaesthesia — 0.5—2%.
- (b) Infiltration anaesthesia — 0.05%.
- (c) Spinal anaesthesia — 0.01—0.02 g/4 ml of C.S.F. with adrenaline

Monocaine or Butethamine HCl is an ester of PABA and is similar in action to procaine but with very poor surface absorption and hence useless. It is more potent and toxic than procaine and duration of action not very long. *Used* in dentistry occasionally—1-1.5% block, infiltration and spinal anaesthesia.

ALLIED TO STOVAINE

Benzocaine. 'Ethyl amino benzoate', an insoluble powder; 1/20 as toxic as cocaine—erythema, oedema.

Uses. (a) 0.3-0.6%/OS for *gastric* irritation. (b) Dusting powder or 5% ointment for painful conditions.

Orthocaine. Methyl-meta amino-oxybenzoate; insoluble powder and also local analgesic effect.

Dose. 20-45 mg; 10% ointment for lacerated wounds. Also used in dental practice.

Butescin Picrate. An antiseptic and local anaesthetic. 1% solution, is used in ophthalmic practice.

OTHER COMPOUNDS

Nupercaine. Also known as *Percaine*—is a quinolene derivative. It is 6 times more toxic but 12 times more potent than cocaine and has rapid absorption, durable action. It is decomposed by alkalis. It does not cause habit formation but occasional convulsion.

Uses

- (a) Infiltration anaesthesia—1 : 2000 to 1 : 1000 with 0.1 ml. of adrenaline per 10 ml. of solution.
- (b) Surface anaesthesia—1-2%, which is equivalent to 5-10% cocaine.
- (c) For urethra and eye—0.2% to 1% solution.
- (d) It is highly potent and best spinal anaesthetic in 4-12 mg. dose, 0.5% in NaCl sol. Anaesthesia lasts for 6-12 hours.

Lidocaine or Xylocaine. Is a dimethyl acetamide derivative, suitable for surface and injection anaesthesia. 0.5%—2% solution, used in dentistry with adrenaline 10^{-5} concentration.

Quinine+Urethane. Is sometimes used for haemorrhoids and pruritis ani. Concentration above 10%, produces necrosis.

SCOPE OF USE

With newer discoveries, and techniques considerably extended, most of the major and minor surgical operations can now be performed with

these agents, without the help of general anaesthetics by using the following techniques:

Surface Anaesthesia. It is restricted mostly to mucous membrane. Less soluble groups of local anaesthetics are the compounds of choice.

Infiltration. (a) Procaine and not Cocaine, is the drug of choice. (b) Combination with hyaluronidase, the spreading factor, helps in the infiltration process. (c) Blocking infiltration process is carried out by crossing the plane in different areas. In this way, intercostal spaces can be anaesthetised for thoracic operations.

Block Anaesthesia. This is akin to the physiological section of the nerve and procaine again is the drug of choice. The block may be (a) Intra-neural. (b) Paraneural, or (c) Paravertebral. This last is an extensive block permitting bladder, prostate and perineum operations.

Spinal Anaesthesia. This aims at anaesthetising the nerves at the subarachnoid space, the level of anaesthesia being influenced by: (a) Site of injection, (b) Amount of fluid injected, (c) Force of injection, (d) Position of patient and (d) Specific gravity of fluid—hypobaric, isobaric, hyperbaric. The first two spreading more easily.

Epidural Anaesthesia. Extensive block can be produced up to chin, without affecting respiration and circulation. Injection is made into epidural or intervertebral space for acting on nerve roots. Drug diffuses through intervertebral foramen along the perineural sheaths. It does not spread up to medulla.

Caudal Anaesthesia. (a) Another type of epidural anaesthesia, in which the fluid is injected into the sacral canal through the sacral hiatus. Drug remains in epidural space—duramater and vertebral canal. It is safer than spinal anaesthesia. (b) It is particularly useful for pelvic operations—birth canal, perineum.

Special Merits. (a) Complete muscular relaxation with abolition of pain and without loss of consciousness. (b) Patients with cardiac and pulmonary disease and diabetics, who do not stand general anaesthetics well.

Dangers. (a) Respiratory paralysis. (b) Headache, nausea, vomiting. (c) Chemical meningism, occasionally. (d) Hypotension due to paralysis of sympathetic fibres in the thoraco-lumbar region.

THERAPEUTIC ABSTRACT

SURFACE ANAESTHESIA	Cocaine HCl	(a) Eyes 2-4% (b) ENT 5-10%
	Butocaine or Butyn	(a) 2% sol. for eye (b) 1% Ung. for skin
	Orthocaine	Cream or Ung. 10% for relief of anal fissures
	Benzocaine	5% oint. for painful skin
	Butescin picrate	1% sol.—burns and ophthalmology
	Xylocaine (Lidocaine)	4%-6.4%. E.N.T.
INFILTRATION ANAESTHESIA	Procaine	2% with adr. S.C. inflt. & nerve block
	Monocaine HCl	1-1. 5% for dental nerve block
	Lidocaine (Xylocaine)	$\frac{1}{2}$ to 2%
SPINAL ANAESTHESIA	Nupercaine	0.2%
	Stovaine	Upto 5% with Ephed. 50 mg. I.M
	Lidocaine (Xylocaine)	5%

1. In Spinal and epidural anaesthesia, the nerve roots are blocked at the point of their exit from the intervertebral foramina. Sensory fibres are affected first, followed by sympathetic and motor fibres. Full effect is usually established after 10 to 15 mts.

Procaine hydrochloride, *dibucaine* or *nupercaine* and *lidocaine* are commonly used. *Nupercaine* produces analgesia, lasting for about 2 to 2½ hours. and therefore preferred in longer operations.

Fall of blood pressure occurs after spinal analgesia because of blocking relaxation of sympathetic fibres. The fall is proportionate to the level of the block, and serious cardiovascular changes can occur if the block is high enough to involve the thorax and carotid sinus reflex. Hypotension is combated by the use of sympathomimetic drugs like *ephedrine*, *mephenteramine*, *methyl amphetamine* (methedrine) *methoxamine* and *nor-epinephrine* (*noradrenaline*). They are used intramuscularly or intravenously depending upon the degree of hypotension.

2. Extradural or epidural analgesia or caudal block is accomplished by 1.5% *Lidocaine* (xylocaine) and the dose varies from 12 to 30 ml. This block reduces the hazard of nerve damage. Recently, continuous epidural anaesthesia by means of a polythene catheter placed in the extradural space, is being used to prolong the duration of analgesia.

Therapeutically, spinal or epidural anaesthesia is indicated in *eclampsia*, *cardiospasm*, *peripheral vascular pain* and for mitigating *labour pains*. It is also used, as a test, to assess the effect of sympathectomy in *peripheral vascular disease*.

3. Of the various local anaesthetic agents, *Cocaine* which was extensively used in Ophthalmology, has been replaced by *anaesthaine* and *lidocaine* for the surgery of ear, nose and throat. These two drugs are preferred for surface analgesia as the action is quicker and analgesia more intense.

4. *Procaine hydrochloride* has been administered intravenously as an analgesic in the treatment of burns, arthritis and intractable neuralgia. Recent studies have shown that its use is not without hazard and in myasthenia, thyrotoxicosis and patients on digitalis therapy, intravenous procaine can spell disaster.

5. *Therapeutic nerve blocks* have been extensively used in various conditions necessitating pain relief. In *trigeminal neuralgia*, injection of alcohol in the sensory root of the trigeminal nerve gives prolonged relief. *Sympathetic blocks* are also frequently used as indicated below:

(a) *Stellate ganglion block* in thrombosis, embolism and spasm of vessels of the arm, head and neck ; Causalgia of upper limb ; auriculo temporal syndrome, tinnitus, some cases of eighth nerve deafness.

(b) *Thoracic sympathetic block* in (i) Angina pectoris. (ii) Biliary colic. (iii) Pancreatic pain in acute pancreatitis.

(c) *Lumbar Sympathetic block* (i) Peripheral arterial disease, (ii) Traumatic vasospasm. (iii) Acute arterial occlusion. (iv) Delayed healing of fractures. (v) Trophic ulcer. (vi) Causalgic states.

CHAPTER

21

PSYCHOPHARMACOLOGY

PHYSIO-BIOCHEMICO-PHARMACOLOGICAL CONSIDERATIONS; DIFFERENT GROUPS OF DRUGS AND THEIR PLACES IN THERAPEUTICS

[With the special advances in our knowledge of CNS and the role of reticular formation, with its antagonistically acting *ergotropic* and *trophotropic* systems, as well as the working of local hormones, it has been possible to explore better this system with a battery of newer techniques, including EEG studies and drugs which can produce psychic disturbances, as pharmacological tools and others which alleviate the same. The former are known as *hallucinogens*, the latter *tranquillisers* and a third group—*psychoanaleptics* or mood elevators. All these are included in the new branch *psychopharmacology*.

Mescaline, *Cannabis indica* and LSD₂₅ produce gross thinking disturbances, disorientation and hallucinations while, Rauwolfia alkaloids, phenothiazine, meprobamate and benactyzine act as *tranquillising agents* and used in schizophrenia, paranoia and anxiety states. The *psychoanaleptics*—iproniazide, deanol, nialamide are used as *mood elevators* in depressive psychosis and melancholia.

The actual status of these drugs has yet to be carefully established but a good start has been made in this unexplored field, even as palliative measures for the mentally ill, for whom, no drug could even be imagined in the past.]

A special branch of study, referring to the mentally ill, has come into existence in recent years. It is because of our inadequate knowledge of mental diseases and its increasing incidence in our present-day civilisation that special attention is being given to this study during the past few decades and consequently, psychopharmacology, psycho and neuro-chemistry and experimental psychiatry, have now emerged as distinct disciplines for advancing our knowledge.

Physio-Anatomical Considerations. The uncertainty of drug action on the C.N.S. is due to the complexity of brain structure, not only in any particular individual, but from individual to individual and in different species of animals, at different stages of evolution.

The physio-anatomical considerations of C.N.S. have already been discussed but the Reticular formation deserves a special mention, as it

is primarily concerned with the psychopharmacological aspects of the problem.

Reticular Formation. This extends from medulla to diencephalon. The *ascending reticular formation* has a neuronal network, receiving diffuse impulses and relaying them to the cortex. It is supposed to have important coordinating functions and is said to control consciousness. It has lots of afferent and efferent connections with other parts of the brain. It consists of antagonistically active parts:

(a) *Ergotropic System.* (i) Coordinating the sympathetic with C.N.S., (ii) Producing wakefulness, behavioural pattern and (iii) Preparing the body for positive actions—arousal, sympathetic, somatomotor and psychic activities.

(b) *Trophotropic System.* (i) Integrating the parasympathetic and somatomotor actions and behavioural patterns of *recuperative nature*—drowsiness and sleep, increased parasympathetic actions, decreased muscle tone and lowered responsiveness to stimuli, the two systems being in continuous opposition, the resulting level of activity ranging from tropho to ergotrophic nature.

Synaptic Transmission. As in the peripheral and the A.N.S., local hormones play important part in the functioning of, specific regions of the C.N.S. ACh, catecholamines, serotonin, GABA are selectively concentrated and by affecting their individual concentrations, alteration of brain and behavioural functions, can be achieved.

Acetylcholine. Unlike in peripheral p-sympathetic and skeletal muscular systems, its role in C.N.S. is not yet fully established.

(a) It is selectively concentrated in basal ganglia, cortex and ventral horn cells of spinal cord, but not so in cerebellum.

(b) It produces no C.N.S. action when given I.V. due both to destruction and non-crossing of the blood brain barrier, being a quaternary ammonium compound. Given intraventricularly or by intracarotid route, it causes C.N.S. stimulation.

(c) ACh. content of rat brain increases in sleep and yet it is liberated more during activity. This contradictory condition is explainable by the fact that stimulation of one part of the brain may be associated with the depression of another.

(d) Atropine affects C.N.S. action. It is postulated that ACh. is concerned with the spontaneous rhythmic activity of neurones, as it is with the rhythmicity of heart.

Catecholamines. Noradrenaline and dopamine are present in brain, chiefly in hypothalamus. Their synthesis in C.N.S. is inadequately known. They are destroyed mainly by MAO. (a) Nor-adrenaline is the neuro-hormone for the *ergotropic* division. (b) Intraventricular adrenaline causes unconsciousness, while noradrenaline does not have this effect. (c) Drugs liberating noradrenaline from hypothalamus cause sympathetic discharges and piloerection. (d) Drugs preventing catecholamine destruction—e.g. MAO inhibitors, cause *elevation of mood*. (e) Drugs depleting noradrenaline from hypothalamus (Reserpine), affect behaviour. (f) Sympatholytic drugs produce C.N.S. stimulation.

5-Hydroxy Tryptamine (Serotonin) : It has already been dealt with in the chapter of Local hormones. In C.N.S., it acts as a transmitter of the ergotropic part of the reticular formation. Given I.V., it does not cross blood-brain barrier, but given intraventricularly, causes lethargy, drowsiness, flaccidity of muscles, licking movements and increased respiration. Its role in the C.N.S. is not fully established. Depletors like reserpine effect behaviour. But other drugs, not depleting 5-HT, have also similar actions. LSD₂₅ which antagonises 5-HT, causes psychosis.

Gamma-amino butyric acid-(GABA) : As already discussed, it is present in mammalian brain extract, and seems to be an important regulator of the inhibitory activity and has been suggested to be an *inhibitory transmitter* in the C.N.S.

Pathological Considerations. In spite of active research, mind still remains almost unfathomable. The behaviour of a person can depart from the accepted normal in many ways. Some of these deviations, as in genius or saint, can neither be fully understood, nor treated, some of the aberrations of behaviour, which can be treated, are:

Mania or Depressive States. With too much or too little overall behaviour—hallucinations, delusions, obsessions, confusions and illusions; responding to stimuli not actually present in the environment, responding inappropriately or seeing or feeling a thing, which does not exist. Abnormal emotional manifestations, as in anxiety states, are also present.

These various manifestations, existing isolated or combined, can be categorised as following syndromes:

Neurosis—exaggerated or abnormal feeling and responses to minor stimuli, with excessive neuro-activity and anxiety.

Psychosis—comparatively major disorder with gross behavioural disturbances—physical and mental and even megalomaniac tendency and suspicion.

Schizophrenia—An offshoot of psychosis with thinking disturbances, introspection, split personality, suspicion of surroundings.

The drugs producing or alleviating these condition are:

Hallucinogens—psychotomimetic or psychodysleptics produce thinking disturbances, leading to hallucinations, delusions and also catatonic states. **Psychoanaleptics**, elevate mood and make people feel happy.

CLASSIFICATION

<i>Hallucinogens</i>	<i>Mescaline</i>	<i>Cannabis, LSD₂₅</i>
Tranquillisers	Rauwolfia alkaloids	Reserpine, deserpidine, rescinnamine
	Phenothiazines	Dimethyl amines—chlorpromazine. Piperazines—compazine, trifluperazine, Piperidines—mepazine, Thioridazine.
	Alkyl diols Diphenylmethanes	Meprobarbate, phenzlycodal. Benactyzine, atarax or hydroxygins
Psycho-analeptics	MAO inhibitors	Iproniazide, isocarboxazide, nialamide, phenelzine
	Others	Deanol, imipramine

Mode of Study. Imperfectly developed and mostly qualitative.

- (1) Effect on normal behaviour : Web-spinning in spiders, fighting response in siamese fish, calming and taming effect in monkeys and siamese cats, effect on shamrage.
- (2) Antagonism to drug : Induced hyperactivity by hallucinogens and study of tranquillisers in rats and mice.
- (3) Effect on conditioned reflexes

Reactions learned for avoiding unpleasant stimuli or obtaining rewards—pole climbing, pecking response, crossing of compartments by rats and pigeons.

- (4) E.E.G. Changes

Drug induced aroused or 'model psychosis' in animals and human volunteers.

Mode of Action. Three different mechanism: (a) By altering the concentration of neurotransmitters in specific areas: (i) Tranquillising effect of reserpine from depletion of 5-HT. (ii) Mood elevating effect of MAO inhibitors from increase of noradrenaline in brain. (b) By reducing energy supply (glucose and ATP) and thus decreasing neural activity—chlorpromazine inhibits cerebral oxidation and ATP synthesis. (c) By affecting reticular formation and disturbing normal sleep-wakefulness rhythm—*chlorpromazine* inhibits E.E.G. arousal and *reserpine* E.E.G. patterns.

HALLUCINOGENS

As stated earlier, these drugs produce gross thinking disturbances, disorientation and various types of hallucinations and even cataleptic and hysterical manifestations, giving an impression of being possessed of supernatural powers. The important members are:

Mescaline. An alkaloid of *Peyote cactus*, growing in Mexico and South America, producing intoxication, disorientation of time and space, vivid visual and auditory hallucinations, anxiety, tremors and schizophrenia like conditions. Action lasts for 6-9 hours. Dose 200-500 mg and used only as a *pharmacological tool*.

Cannabis Indica. (a) Also known as *hashish* and *marihuana*, grows in India, Egypt and S. America. It is a habit forming drug, available in 3 forms—*Resin* or *Charas*, flowering tops of *ganja* and leaves or *bhanga*, used as smokes and drinks. (b) It possesses some sedative, antispasmodic, hypnotic and also hallucinogenic properties, due to *cannabinol* or *tetrahydrocannabinol*, as active principle. (c) Actions resemble opium and alcohol on the C.N.S.—euphoria, feeling of well-being, hallucinations, untrammelled imagination, mental exhilaration, impulsive behaviour, delirium and mania, (d) The drug has no place in modern therapeutics and because of its addiction liabilities, it is a danger to the society.

LSD₂₅ (d-lysergic acid diethylamide):

This wonder pharmacological tool was discovered by Albert Hoffman, in 1943, and its essential structure d-lysergic acid, observed to resemble ergonovine. The thinking disturbance, observed after ergotised rye consumption, was also accidentally found out in his own case, with symptom complex of vertigo, hallucination and depersonalisation.

Since then, much work has been done with this potent drug and its efficacy, in as low a concentration as 1 µg/kg, established.

LSD₂₅ is an *Indole* derivative, obtained from Ergot. It produces auditory and visual hallucinations and marked thinking disturbances but unlike in schizophrenia and paranoia, contact with reality is not lost. The drug produces tolerance in 3-7 days.

It is believed to block specifically cortical inhibition and also sympathetic intra—cortical circuits and/or sympathetic projections, to and from the telencephalon.

Though one of the best pharmacological tools for inducing 'model psychosis' in volunteers and also psycho-catharsis in schizophrenics, bringing out hidden information for diagnosis and therapeutic measures, the *hazards* of LSD₂₅ administration in normal and psychopathic patients, as reported by Cohen (1960), should not be minimised. These are—euphoric states, followed by periods of depression, states of confusion, tenseness, panic episodes and also suicidal tendencies.

As a diagnostic tool, it should not be indiscriminately used and when used, adequate precaution by selection of cases, measures for counteracting or reversing the effect and above all, nursing facilities against sudden upheaval of emotions, should be easily available.

TRANQUILLISING AGENTS OR ATARACTICS

Ataraxis literally means "*perfect calmness*", free from confusion and anxiety and the drugs which produce this effect without appreciable depression and alteration of mental activity, are known as *ataraxics*.

These drugs, though sometimes indicated for highly strung population of today, are producing alarming problems in some of the advanced countries like U.S.A., in which, it is reported that nearly 8 million people are being medicated with chlorpromazine, similar number of doses of meprobamate every month and 18 million prescriptions for tranquillisers in 1955. The immediate and remote toxic effects of these drugs should not be lost sight of.

Mechanism of Action : not definitely settled. More than one mechanism is involved, in cases of different tranquillisers. (a) Depression of hypothalamus—the seat of emotion and coordination—fight and flight. (b) Depression of ascending reticular activating system and prevention of alerting reaction or arousal pattern. (c) Mediation through ergotropic inhibition or trophotropic stimulation, e.g. chlorpromazine and reserpine respectively, perhaps through their action on 5-HT and catecholamines.

RAUWOLFIA SERPENTINA

This wonder drug has long been used in India as an insanity cure (*pagal ki dawai*) and has now established a definite status for tranquillising effects in neurotic, hypertensive patients.

Action. (a) The sedative effect is attributable to the resin fraction, containing the active alkaloid *reserpine*, but it differs from other C.N.S. depressants, as it is associated with a fall in B.P., bradycardia, miosis, respiratory inhibition and centrally produced hypothermia. (b) It does not prevent cariazol or picrotoxin induced convulsions. (c) It, however, causes a marked change in the behaviour pattern, in as much as monkeys lose their normal aggressiveness under the influence of Reserpine. Similarly hyperdynamic patients experience a decreased drive and do not run after things so readily.

Dose. Reserpine—0.75—1.5 mg/day. Serpina containing 0.1% reserpine—1 gm/day/os.

Side Effects. Restlessness, lethargy, fatigue, nasal stuffiness, postural hypotension, odema, Parkinsonism, salivation, increased appetite, also suicidal tendency.

Uses. (a) Hypertension—*mild form*—0.05—1.5 mg/day; *severe form*—0.25—0.5 mg/day with some potent hypotensive. (b) Schizophrenia—manic depressive psychosis and involutional depression. Reserpine causes marked remission of symptoms. In chronic schizophrenia, initially 5 mg. I.M. then 2-8 mg/OS daily, for 3-4 months. Much more useful in acute cases than chronic ones. (c) Delirium tremens—2.5 mg. I.V., to be repeated after 3 hours. (d) Neurosis and anxiety states—particularly accompanied with palpitations and tachycardia, gives immediate symptomatic relief probably due to depression of central sympathetic over-activity. (e) Parkinsonism—Reserpine in 0.1—0.25 mg. doses, a good adjuvant to other known remedies.

CHLORPROMAZINE

Also known as '*largactil*, or large spectrum drug, it is a phenothiazine derivative, possessing several interesting pharmacological properties, of which, its central sedative effects, are the most important.

Chlorpromazine HCl is a greyish-white crystalline, water soluble powder, available as 10-25 mg. tablets or 0.8% solution in ampoules.

Action. (a) Selective depression of C.N.S. particularly of the reticular formation. It depresses cellular activity and produces mild sedative and hypnotic effect. E.E.G. changes resemble those in normal sleep. (b) With moderate doses, it produces drowsiness, depression of condition and postural disturbances and in higher doses, even anaesthesia and muscular relaxation, as in "*lytic cocktail*". (c) The action of morphine and anaesthetics is potentiated, while that of analeptics, acting on the brain stem, is antagonised. The action of strychnine on the cord remains unaffected. (d) It acts as an antiemetic by acting on the C.T.Z. in the medulla and hence it is used in '*Motion sickness*'. (e) It inhibits the sympathetic diencephalic centres preventing the responses to stress, thus maintaining the constancy of the internal environment. (f) It also causes pronounced B.P. fall with compensatory tachycardia.

Dose— 50-100 mg. orally, to be gradually increased to 2-3 gm. It can also be used I.M.

Side Effects. Hypotension, hepatitis, dermatitis, agranulocytosis and Parkinsonism.

Uses. (a) Psychomotor states of agitation producing considerable relief. (b) Schizophrenia with catatonia and paranoia—dramatic reversal of symptoms. (c) Is of moderate value in depressive states. (d) Senile and arteriosclerotic patients, with agitation, combativeness and confusion. (e) Morphia and alcohol withdrawal states.

MEPROBAMATE

Also known as *miltown* or *equanil*, is a drug of great promise in the relief of anxiety and tension states. Chemically, it is methylpropylpropanedial-dicarbamate, with a bitter taste.

Actions. (a) Possesses central effects on thalamus in relieving or calming the physiological components of anxiety. (b) Reduces fear, aggressiveness, hostility, tremulousness and develops a sense of well-being. (c) Blocks multineuronal synapses, so that reflex actions are reduced or blocked and muscle relaxation produced. Incoming stimuli are temporarily modified and the individual can show control over emotions.

Side Effects: Drowsiness, muscular weakness, gastric discomfort and skin rashes.

Uses. Available in the form of 400 mg. Tab.—one tablet QDS. after meals, in anxiety and tension states, with headache and insomnia.

PACATAL OR MEPAZINE

It is a phenothiazine derivatives with two times more potent tranquilising effect than chlorpromazine, but a weaker hypnotic. It produces mild euphoria and its parasympatholytic effect—produces dry mouth, dilated pupil, atony of gut and bladder. It possesses synergistic action with chlorpromazine, while mutually antagonising the side effects of each other.

Dose: 100 mg. tablet tds., may be increased to 300 mg. tds.

Uses: Asthenic individuals with maniac episodes.

BENACTYZINE (SUAVITIL)

It belongs to the diphenyl methane group; the HCl salt is a white, crystalline powder, soluble in water.

Actions. (a) Diminishes response to stress and strain and relieves anxieties. (b) Anticholinergic and local anaesthetic action. (c) Quinidine like action on heart.

Dose. 1-2 mg. tds.

Uses. Anxiety and obsessional states, psychogenic asthma, eczeme and alcohol addiction.

PSYCHOANALEPTIC DRUGS

As the name suggests, they comprise of a group of drugs which elevate mood and used in depressive states of mind. As this action is related to the inhibition of MAO, the physiological role of this enzyme, along with the inhibitors, will be discussed.

Monoamine Oxidase (MAO). An enzyme, discovered by Hare in 1928; it catalyses the deamination and oxidation of monoamines, catecholamines & 5-HT. It is widely distributed in liver, kidney, pancreas, suprarenals, heart, blood vessels, brain and tissues with adrenergic innervation. It is also present in the sympathetic ganglia and is mainly localised in the mitochondria and microsomes.

It limits the actions of adrenaline and noradrenaline at the adrenergic nerve endings and of 5-HT and noradrenaline, in certain regions of the brain. Its inhibition may cause accumulation of these substances in the tissues, with consequent changes in the functioning.

MAO INHIBITORS

Iproniazide or Marsalid. (a) A hydrazide derivative and potent inhibitor of MAO, it causes elevation of mood, increased physical activity and resistance to fatigue. Action starts after a latent period of a week or more. The effect is probably due to the inhibition of MAO in brain, with subsequent increase in noradrenaline concentrations. (b) It produces side-effects like constipation, postural hypotension, xerostomia, sweating, dizziness, and liver damage. (c) It is used in doses of 50 mg. tds. in the treatment of depressive states and also for stimulating appetite and weight gain in debilitated peoples.

Isocarboxazid or Marplan. It is more potent as a MAO inhibitor than Iproniazid and as potent as Iproniazid in relieving depressive states with fewer side effects. The oral dose is 30 mg/day.

Nialamide or Niamid. As potent as Iproniazid in inhibiting MAO and is used in depressive states, in doses of 75 mg/day, in divided doses. The drug may produce nervousness, insomnia, lethargy, vertigo and jaundice.

Phenelzine or Nardil. (a) It is also a potent MAO inhibitor which is used as an antidepressive agent. It elicits sympathomimetic effects—pressor response, contraction of nictitating membrane and mydriasis. (b) It preferentially inhibits MAO in brain and is used in depressive states, in doses of 15 mg. tds.

The *side-effects* are hepatitis, postural hypotension, nausea and constipation.

Deanol. A C.N.S. stimulant, used as a mild antidepressive agent, counteracting lassitude, fatigue, depression and over-sedation. It is used in chronic fatigues and mild depression, in doses of capsules of 25 mg., 1 to 3 times a day.

Imipramine or Tofranil. (a) A thymoleptic agent producing uplifting of spirits. The drug is used as HCl salt and is absorbed readily from the oral and parenteral routes and is uniformly distributed. (b) In addi-

tion to its antidepressive effect, it also exhibits a weak anticholinergic, transient hypotensive and spasmolytic action. (c) Its mechanism of action is not through the inhibition of MAO but probably through the sensitizing of central adrenergic synapses. (d) It is indicated as a specific treatment of depression. *Dose*—100 mg/day OS/IM, increased by 25 mg every few days, up to 200 mg/day.

Side Effects. Skin eruptions and tremors and is to be used with caution in patients with increased intra-ocular pressure.

It is one of the safest antidepressive agents and is suitable for use in depressive states, irrespective of their specific diagnostic classification.

THERAPEUTIC ABSTRACT

Hallucinogens or psychodysleptics	Pharmacological tools or psychocathartics	LSD ₂₅ , mescaline
	Thinking disturbances—schizophrenia, Paranoia	Reserpine, chlorpromazine
	Maladjustment & anxiety states	Chlorpromazine, mellaril
Psycholeptics or Ataractics	Antiemetic and lytic cocktail	Chlorpromazine, trifluoperazine
	Spastic skeletal muscle disorders	Meprobamate
Psychoanaleptics	Depressive mental states, mild depression, depressive psychosis, melancholia	Imipramine, amitriptylene, niamid, marsilid, dexedrine + amylobarbitone

These psychopharmacological agents find their limited scope of use for the following:

Psychocatharsis. The psychodysleptics or hallucinogens, are occasionally used with precaution, for psychoanalysis purposes and also for evaluation of antagonistic psychopharmacological agents.

Psychoneurosis. For *acute anxiety states*, sodium amobarbital—250 mg, or alternatively phenobarbitone—130 mg, is used. For *chronic states*, meprobamate—200-400 mg or chlordiazepoxide—5-10 mg t.d.s., may be used. If the patient is highly irritable, phenobarbitone—30 mg for 2-3 weeks, may be tried. Ordinarily, phenothiazines are not recommended unless the patient is refractory to the above therapy.

Psychasthenia. A condition characterised by obsession, morbid fear and suspicion, is also known as *obsessive, compulsive neurosis*. Its management comprises of judicious use of—(a) Psychotherapy, (b) E.C.T. and insulin therapy and (c) Use of tranquillisers—but all mostly with poor results.

Maniac Depressive Psychosis. For this, a combination of psycho and pharmacotherapy is indicated—(a) *d*-amphetamine and amobarbitone—2.5 mg, t.d.s. for 3 days, (b) Imipramine or amitriptyline—25-50 mg, t.d.s., for a few days, if no improvement with the former, (c) E.C.T. and Insulin shock may be tried as last resorts, (d) In general, MAO is not recommended for depressive neurosis. Improvement is expected only in functional types of cases.

Schizophrenia. Being a very complex condition, its management is extremely difficult. During the psychotic phase, the patient is to be hospitalised, and psychiatric treatment advocated. Evaluation of drug effect is difficult because of the uncertainty in the course of disease itself. *E.C.T.* and *metrazol shock therapies* have been found to produce remissions in 29%, tranquillisers in 34% and insulin therapy in 43% of patients. With other methods of treatment—custodial, lobotomy and psychotherapy, the results are not very stimulating also.

CHAPTER

22

SEDATIVE, HYPNOTICS AND ANTICONVULSANT DRUGS

SELECTIVE AND NON-SELECTIVE ACTION IN CONTINUUM. CLASSIFICATION, CHEMICAL NATURE. TOXICITY AND ADDICTION LIABILITIES

[The depressants of CNS can also produce other types of action than general anaesthesia, which last, is an extreme degree of depressant action of a generalised nature. Some of them lessen the irritability of brain, quieten the patient and suppress non-specific convulsions and are known as *sedatives*. Others make the patient less aware of environment and produce actions resembling natural sleep for a specified period. These drugs are known as *hypnotics*. They should act quickly and produce refreshing sleep, without any side-effects or risk of drug habit.

The important *sedatives* comprise of bromides, hyoscine HBr., barbiturates in small doses, chlorpromazine, urethane and chloretone. The *hypnotics* constitute a much larger group, under the subheads of—(a) Anodyne—morphine, (b) Non anodyne—chloral, paraldehyde, barbiturates and (c) Newer drugs—doriden, dormison, perichlor, noludar etc.

The sedatives are indicated in spasmodic, hyperirritable and convulsive disorders for prolonged action, while the hypnotics are used in insomnia cases mostly, for inducing sleep for 4-6h., generally.

The barbiturates constitute a very special group and are classified as—(a) long acting, (b) medium acting, (c) short acting and (d) ultra short acting compounds. Long acting phenobarbitone is mostly used in grandmal epilepsy and the ultra short acting thiopentone for I.V. anaesthesia. The intermediate and short acting groups—dial, amytal, nembutal etc are indicated for provoking hypnosis, obstetrical anaesthesia and premedication in general anaesthesia. They have all their limitations because of the need for prolonged use and also habit formation. That is why, the newer drugs are in demand with probably no special advantage over the older members.]

It is possible to induce a lesser degree of depression of C.N.S. than in the case of general anaesthesia. This may result in sedation or hypnosis and even anticonvulsant and antiepileptic action, depending on the areas affected.

Sedatives lessen the irritability of practically all the parts of the C.N.S. in a general nonspecific manner and the patient, though awake, has a lessened degree of cortical excitability.

Hypnotics suppress cerebral activity so much as to make the patient less aware of environment and produce condition resembling natural sleep.

In case of anticonvulsants, the depression may again be of a generalised nature affecting the cortex, spinal cord etc., but in the case of antiepileptic action, preferably of the motor cortex.

Hypnotics act more quickly than sedatives, and their depressant action is mainly on the thalamus and cortex, though other parts like medulla may also be depressed.

The difference between a sedative and hypnotic is sometimes a quantitative one, a small dose of hypnotic can act as a sedative, toxic dose of a sedative, as hypnotic and sufficiently large dose of hypnotic can produce all the characteristics of general anaesthesia, though with a narrow safety margin.

Physiology of Sleep. (a) Sleep is nature's mechanism for forced rest for varying periods—6-8 hours per day in adults, more in the young and less in the old. Napoleon's record of 3 hours/day and even 1/4 hour on the horse back. In sleeping sickness, the picture is reversed. (b) During sleep, the parasympathetic appears to be more active than the sympathetic nervous system, producing myosis, hypotension, bradycardia, bronchial constriction, hypersecretion in the G.I. Tract and increased peristalsis.

Theories of Sleep. (a) Sleep—regulated by a centre or centres in the hypothalamus. It can be produced by stereotaxic technique, by experimental stimulation of hypothalamus or by the pathological lesions, as in encephalitis lethargica. (c) Sleep is a conditioned reflex, elicited by comfortable surroundings and conditions—Pavlov's theory. (d) Impulses from the reticular formation activates the cortex and subcortical regions producing awakening. Inhibition of these produces sleep. (e) Injection of ergometrine or ACh into the third ventricle, produces sleep (Hess 1927, Dikshit 1934).

Insomnia. It is a state of awakening in spite of fatigue and may result from any of the following causes: (a) *Psychic*—worry, anxiety, mental preoccupation, change of environment. (b) *Physiological stimuli*—noise, uncomfortable temperature and improper ventilation. (c) *Pathological*—pain, organic lesions of heart and lungs. (d) *Chemical*—cortical stimulants—caffeine, amphetamine, dextedrine.

Types of insomnia often differ considerably clinically from one individual to another. (a) Some patients, due to cortical excitability,

as in neuroses, have difficulty in going to sleep, but once asleep, they can sleep for the required period. Such patients require a short acting hypnotic. (b) Some patients cannot remain asleep for a long time due to painful, inflammatory conditions. They benefit by use of medium acting hypnotics. (c) Some patients have only fitful and restless sleep throughout the night and would require long acting hypnotics.

Method of Evaluation. (a) Determination of 'sleeping time' in laboratory animals—rats, guinea pigs. (b) Determination of "stand still point" in fish. (c) Cortical oscillography or encephalography, denoting potential changes.

An Ideal Hypnotic. (a) Smooth and prompt onset, definite period of duration, smooth awakening and no preliminary excitement nor after-effects. (b) No tolerance, no addiction, but wide safety margin.

As alcohol produces initial excitement, morphia and paraldehyde—marked after-effects and addiction and sulphonals, unpredictable action, they are not suitable for use as hypnotic.

CLASSIFICATION

<i>Sedatives</i>	<i>Potassium bromide hyoscine hydrobromide, barbiturates (small doses), urethane, chloretone</i>
Anodyne	Morphine and morphine substitutes
Non-anodyne	(a) Chloral -chloral hydrate, chloretone, chloralose (b) Aldehyde— paraldehyde (c) Alcohol—bromethol, ethyl alcohol, placidil (d) Sulphonal—sulphonal, trional, tetranol
Hypnotics	(e) Ureides- barbiturates, carbromal
Newer Drugs	A large number of synthetic drugs of various chemical groups—carbamic acid, piperinedion, methyl pentanol, pentaerythriton, chloral, carbromal—yielding proprietary preparations—Valmid, doriden, dormison, Perichlor, adalin, noludar—each vying for clinical superiority to patients who appreciate any new drug as a change.

BROMIDES

There are several and collectively known as *Inorganic bromides*.

Dose : 0.3—2.0 gm. '*Triple bromide*' is a mixture of sodium, potassium and ammonium bromides and may be used as a sedative.

Metabolism. It is very similar to chlorides in absorption from G.I. tract distribution in extra-cellular fluid and slow excretion (20 days) in urine, perspiration, saliva and milk.

All the halogens are treated alike by the system without discrimination. As serum concentration of bromide is less than that of chloride, it is excreted. This is known as *bromide-chloride equilibrium*.

Actions. Only a few of real value, the rest are all useless side-effects. (a) sedation and depression of cortical centres, including motor areas. but no action on pain centre. (b) sedation of irritable heart. (c) Relief of irritating cough, and antispasmodic action on plain muscles.

Toxic Effect. Acute and chronic bromism.

Acute bromism—dullness, amnesia, lassitude, torpor and death.

Chronic bromism—in epilepsy mostly, due to prolonged use, when bromide therapy was in use (a) Increased secretions—lacrymation, coryza, as with Iodides. (b) Bromide rash—acneform, in seboerrhic patients; mostly because of its excretion through the skin. (c) G.I. troubles—anorexia, furred tongue, foul breath, constipation. (d) Bromide psychosis—Impaired thought and memory, slow, sluggish speech, even ataxia.

Treatment. (a) Restricted fluid intake, (b) Sodium chloride—6-12 gms/day, (c) Liq. asernicalis—for skin troubles. Recovery in about 3 weeks.

Uses. (a) Chronic sedation in irritable, spasmodic conditions and anxiety states, (b) Convulsive disorders—limited use.

CHLORAL HYDRATE

A chlorinated derivative of ethyl alcohol, which on hydration gives chloral hydrate.

Colourless, pungent, bitter, mildly volatile crystals, *Sol.* 1:0.25, with alkalis, liberating chloroform. Dose: (0.3—1 G).

Metabolism. (a) Absorption—G. I. tract and rectum. (b) Reduced to trichlorethyl alcohol—the active form. (c) Combined with glycuronic acid in liver and the conjugated form excreted as urochloralic acid in urine, reducing Fehling's solution. When liver detoxicating mechanism fails, it is known as *chloralism* or *chloral habit*.

Action. (a) A local irritant for skin and m.m. causing erythema and vesication. (b) C.N.S. depression-hypnosis in 1-2 hr. (c) No analgesic, nor specific anticonvulsant action. (d) In therapeutic doses, mild V.M. depression and in strong doses, chloroform like arrhythmia.

Toxicology

(1) *Acute*—G.I. irritation. congestion and narcosis.

(2) *Chronic*—Gastritis, skin troubles.

Treatment: In acute condition, by stomach wash and use of analeptics and in chronic conditions, withdrawal, use of stimulants and rehabilitation.

<i>Chloral</i>	<i>Morphine</i>
A quick & refreshing hypnotic	Less refreshing hypnotic
Usually no after-effects	Always headache, confusion and narcosis.
No constipation; little G. . upset	Constipation & nausea.
Does not relieve insomnia from pain	Relieves better insomnia from pain
Does not relieve reflex cough	Relieves reflex cough
May relieve convulsive conditions	Does not relieve convulsive conditions.

Uses. (a) As a pure and simple hypnotic in febrile and nervous types of insomnia. (b) In spasmodic disorders e.g. eclampsia, chorea and whooping cough.

PARALDEHYDE

A polymer of acetaldehyde. It is colourless, transparent liquid of pungent burning taste. *Sol.* 1:8 *Dose:* 2-8 ml.

Metabolism. It is absorbed from the intestine, as well as, rectum and excreted to the extent of 95% through lungs, which may aggravate its inflammatory conditions. It is oxidised in liver.

Action. (a) It is a mild hypnotic, producing sleep in 15-30 mins. which is of short duration. It may sometimes produce initial excitement. (b) It does not depress heart or respiration nor does it possess any analgesic action. It is not toxic for the kidney.

Drawbacks. A safe hypnotic and given parenterally, can sometimes control violent patients even when barbiturates fail. But the drug

is irritant for the G.I. Tract and produces garlic smell in the breath which is very unpleasant to the patient.

Uses. (a) Mainly cardiac insomnia—given in the form of gelatin capsules or glucose saline in the form of enema per rectum. (b) It is also used as anticonvulsant in *status epilepticus*, when other measures fail.

SULPHONES

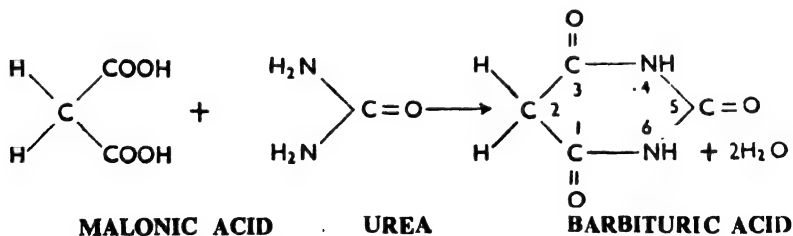
Almost a relic of the past, these are powerful hypnotics but with unpredictable action in respect of onset and duration. They are three: (a) Sulphonal, (b) Trional, (c) Tetronal. Dose: 0.3-1.3 gm.

Because of long duration of action, they were formerly used in mental asylums, for the control of violent patients over prolonged periods.

BARBITURATES

A most effective group of C.N.S. depressant, used extensively for varying purposes: (a) *sedation*, (b) *hypnosis*, (c) *antiepileptic action*, (d) *general anaesthesia*.

Barbituric acid was synthesised by Bayer in 1864, but its first hypnotic derivative i.e. *diethylbarbituric acid*, was introduced into medicine by Fischer and Von Mering in 1903. Since then, nearly 2500 compounds have so far been prepared and the race still continues. The world's production of barbiturates is over 350 tons and over one million people are put to sleep each night by this single group of hypnotic. This may be due to the fast life of high tension of modern days but the alarming point is that the drug is accessible to lay public and its addiction and criminological hazards are on the increase in a larger number of countries.



Illus. XII—Steps in the synthesis of barbitone

Chemistry. Barbituric acid is a '*diureide*', obtained by the condensation of malonic acid and urea, forming malonylurea or barbituric acid.

SAR : Barbituric acid itself is devoid of hypnotic activity. Pharmacologically active barbiturates are obtained by introducing various groups in the 5-5 positions. (a) For optimal pharmacological activity, presence of 4-8 carbon atoms in the substituent groups at 5 positions is necessary. (b) Compounds with alkyl radicles are comparatively stable than the cyclic ones. (c) Length of the side-chain determines the intensity and duration of action—short acting ones having longer chains than the long acting compounds. (d) Replacement of O by S at position 2, produces *thiobarbiturates* which are very readily detoxified and hence short acting. (e) The anticonvulsant action of phenobarbitone seems to be linked to the *phenyl group* at 5 position.

CLASSIFICATION

Groups	Proprietary name	Chemical name	Hypnotic dose mgm.	Uses
Long acting 8-12 hrs.	Veronal	Barbitone	300-600	Animal anaesthesia
	Luminal	Phenobarbitone	60-120	Sedative, hypnotic & antiepileptic
	Phemitone or Prominal	Methyl phenobarbitone	60-120	—do—
Inter-mediate 6-8 hrs.	Dial	Allobarbitone	60-200	Insomnia & anxiety, neurosis states.
	Amytal	Amylobarbitone	100-300	Obstetrical anaesthesia
Short acting 2-3 hrs.	Seconal Na.	Quinalbarbitone Na.	100-200	Premedication anaesthesia
	Phanodorn	Cyclobarbitone	200-400	A quick acting hypnotic
	Nembutol	Pentobarbitone	100-200	—do—
Ultra short $\frac{1}{4}$ - $\frac{1}{2}$ hrs.	Evipan Na	Hexobarbitone Na	300-1000	I. V. anaesthesia
	Pentothal Na	Thiopentone Na	—do—	Control of insulin, metrazol & electro shock convulsions.
	Kemithal Na	Thialbarbitone Na	—do—	—do—but less respiratory depression and less laryngeal spasm.

Preparations. The barbiturates are available in powders tablet, capsule, syrup and elixir forms. They are prescribed alone or in a mixture, with tranquillising analgesic, ephedrine, antihistaminics, spasmolytics and antibiotics. Sodium salts can be used parenterally.

Metabolism. (a) The barbiturates are absorbed satisfactorily from G.I.T. as well as from the site of injection. The long acting ones are absorbed more slowly than the short acting ones. (b) They are distributed fairly uniformly to all the tissues and body fluids and cross blood-brain and placental barriers. Lipid solubility, protein binding and degree of ionisation affect the distribution and fate of barbiturates. (c) Detoxication takes place in liver through the oxidation of radicles at 5 position. Drugs like *chlorpromazine*, *iproniazide* and *imipramine*, prolong the hexobarbital sleeping time by inhibiting the oxidative enzyme. (d) The long acting barbiturates are cleared to the extent of about 50% per day, while the ultra short acting ones 50% per hour.

Action. The main action is on the C.N.S. and the rest are less important.

C.N.S.: All degrees of depression of C.N.S. ranging from mild sedation to anaesthesia. (a) Hypnosis, resembling natural sleep is produced in $\frac{1}{2}$ —1 hour and is due to the depression of the *thalamus*—cortex axis. (b) Analgesic action is nil or insignificant but it potentiates salicylates. (c) Anticonvulsant action shared by all but *phenobarbitone* and *phemitone* show selective action on motor cortex and threshold for electro shock convulsion is considerably raised. (d) Anaesthesia—particularly after I.V. injection of *thio* and *ultra short acting oxybarbiturates*, *Sensory component* is not completely blocked and *laryngeal spasm* and *depression of medullary respiratory centre* quite frequently occurs.

Respiratory system: Potential respiratory depressants, affecting both respiratory rate and rhythmicity, leading to cheyne-stokes respiration—a real danger in I.V. anaesthesia.

Miscellaneous Effects. (a) Reduction of B.M.R. with larger doses, (b) Relaxation of G.I. tone, (c) Anuria and nephritis in acute poisoning, (d) Lack of action on normal hepatic functions, (e) Tolerance and addiction on prolonged use.

Mechanism of Action. Not fully known. (a) depression of ascending reticular formation. (b) uncoupling of oxidative phosphorylation. (c) inhibition of oxygen utilisation and energy utilisation by ATP. (d) biosynthesis of ACh—diminished.

Acute Toxicity. Either accidental or suicidal, the latter not infrequent because of the induction of painless death at 15 times of therapeutic dose level. Sedation and hypnosis with pleasant dreams, leading towards coma. Considerable respiratory and C. V. depression, shock

level B. P., hypothermia, cold, clammy perspiration and death from respiratory failure with or without terminal pneumonia. Its management comprises of—(a) General measures (b) Infusions and (c) Drug therapies.

General measures : (i) Stomach wash (ii) Keeping patients warm (iii) O₂ by nasal or intratracheal intubation with positive pressure (iv) Catheterisation of bladder for measuring 24 hrs output of urine.

Fluid therapy : (i) Saline, glucose saline and 5% mannitol by I.V. drip method, preferably by venesection or venepuncture, in doses of 2-3 litres in 24 hrs., provided the kidney responses are encouraging. (ii) After stabilisation of respiration, B. P., pulse and urine output, nourishment fluids containing special proteins and amino acids should be given either through the intragastric tube or as I.V. fluid.

Drug therapy : The use of analeptics of the type of coramine, picrotoxin and also the erstwhile accepted specific barbiturate antidote-megimide, is now considered almost to be superfluous, as they are poor stimulants of the respiratory centre and do not influence drug excretion.

The recent concepts are to maintain the vital functions—renal, circulatory and respiratory, by ensuring adequate fluid intake and output, oxygenation, electrolyte balance and use of potent diuretics like mannitol for activating the kidneys to work, and facilitating smooth clearance of the drug from body, including its adipose storage depot.

The treatment should also include the use of broad spectrum antibiotics as prophylactic measures for covering up the risks of infection. With all these scientifically designed therapeutic measures, the incidence of fatality has been much reduced provided that the therapy has started not too late and the dose taken has not been excessively lethal.

Megimide or bemegride—is a derivative of glutarimide and a chemical analogue of barbiturates. It was supposed to bring the patient to stabilised physiological states, though not affecting the blood level of barbiturate, nor accelerating its excretion. The drug was given in normal saline I.V. drop at the rate of 1 drop/sec., the total dose not exceeding 1500 mg in any case. Any over-action could be antagonised by *daptazole*. The drug was believed to act by receptor competition. However, with the discovery of mannitol, the use of megimide, as well as of analeptics, has virtually been given up.

Chronic Toxicity. Mostly during treatment of epilepsy. (a) After-meal drowsiness, mental depression, confusion, failing memory. (b) Epigastric pain, diplopia, nystagmus and ataxic gait. (c) Exfoliative dermatitis.

Uses. (a) *Hypnotic*—a palliative in simple nervous insomnia not associated with pain; phenobarbitone $\frac{1}{2}$ -1 hr., pentobarbitone, $\frac{1}{4}$ hour before bed time. (b) *Sedative*—in all cases of hyperexcitability and anxiety states—hypertension, exophthalmic goitre, delirious conditions. Sedative dose about $\frac{1}{2}$ of the hypnotic dose and action starts within a couple of hours as against days with bromides. (c) *Anaesthetic*—basal, general and obstetrical, already discussed. The child may be born with respiratory difficulty. (d) Lastly, anticonvulsant and antiepileptic use. For immediate action, sodium salts of phenobarbitone, phenitone and amytal may be used I.M. or I.V. They have hardly any effect in petitmal epilepsy.

NEWER DRUGS

Besides the above, a number of newer synthetic compounds are available for use as *sedative* and *hypnotic* in recent years. They are designed to eliminate the side-effects, toxic manifestations, narcotic habit formation and make them more suitable for short day or night sedation and hypnosis, singly or as adjuvants to other drugs.

Dormison. Methyl pentanol—an oily liq. of burning taste. *Dose:* 250-500 mg. 3-4 times/day.

The drug is absorbed from the G.I. tract quite easily. It is completely metabolised in the tissues. Its sedative and hypnotic effects are better than those of paraldehyde and it can induce natural sleep in 15-20 mins. which is of short duration of about an hour. It has also been used in preanaesthetic medication and barbiturate resistance cases, but getting unpopular these days.

Doriden. or glutathemide is chemically related to megimide. It induces hypnosis in $\frac{1}{2}$ hr. lasting for 4-8 hours.

It is available in tablets of 0.25 gm., 1-2 tabs. tds. Its toxicity is negligible—nausea, vomiting, dizziness, skin rashes and xerostomia. The drug can also be used for preoperative sedation, induction of twilight sleep and daytime sedation.

Pentaerythritol chloral (Perichlor). A new compound, introduced as *hypnotic* and *sedative* in a dose of 0.5-1 gm and the action is quicker and longer than that of chloral hydrate. *Carbromal* (adalin) a *sedative* and mild hypnotic with less prompt action than barbiturates and also much less toxic and no after-effects. *Dose:* 0.3-0.6 gm caps. as *sedative* in *anxiety states*. *Etheriamate* (valmid)—a mild sedative and hypnotic

with less toxicity. In a dose of 600 mg., it induces to sleep very satisfactorily within 20-30 mins. Action lasts for 4 h. *Ethchlorovynil* (placidil) in a dose of 300 mg, acts as a sedative and hypnotic. *Methypylon*—(moludar):—hypnotic dose. 200-400 mg and for day time sedation—50-100 mg t.d.s.

THERAPEUTIC APPLICATIONS

Besides other uses, these drugs are specially considered for effecting sedation, or hypnosis in a number of conditions detailed hereafter. They are also used in convulsive disorders as a palliative measure.

Sedation. A number of conditions often need the use of sedatives. These are psychic disorders, acute illnesses, myocardiac infarction, thyrotoxicosis, hypertension, peptic ulcer, menopausal syndrome, asthma etc.

Though erstwhile, bromides were the drugs of choice because of their long duration of action, more lately, barbiturates in small doses—phenobarbitone, seconal, amytal and some of the tranquillising agents like equanil, are more in use. The newer sedatives—doriden, placidyl, noludar have been gaining increasing popularity in recent time, because of proclaimed superiority, decreased risk of habit formation and toxicity.

Hypnosis. Depending on the cause and type of insomnia due to pain, organic diseases or toxic conditions, in patients with plain and simple insomnia, who have difficulty only initially to go to bed and once asleep they can continue without any trouble, in such cases, a short acting barbiturate of the type of *Seconal* or *Evipal*, may serve the purpose. In other cases, medium or long acting barbiturates like amytal, phenobarbital, may be useful. Other drugs, which may also be used are *Perichlor*, *Adalin* and *Noludar*.

Convulsive Disorders. These are abnormal states, characterised by irregular, involuntary, jerky movements. They may be associated with sensory disturbances, loss of postural tones and alteration of consciousness. Besides epilepsy, convulsions are frequently seen in tetany, brain trauma, meningitis, uraemia, eclampsia, cerebral malaria, hysteria, drug poisoning, hypoglycaemic states, etc.

The management comprises of—General and Specific measures.

General measures include use of sedatives and anticonvulsants like—

Phenobarbital Na—0.06-0.12 gm. S.C. or I.M. *Paraldehyde*—3-8 ml/rectum. *Chloral hydrate*—0.5-1.0 G/rectum in olive oil. *Mag. sulphate*—25% 0.1-0.2 ml/kg. I.M., in severe convulsions. Anaesthetics like ether, avertin, amytal Na or pentothal Na, may also have to be used.

Specific measures include the treatment of the underlying cause e.g. in *hypoparathyroid tetany*, Ca lactate or gluconate, AT₁₀, VitD parathyroid, extract; *epilepsy* by antiepileptic drugs; *meningitis* by sulphonamides and antibiotics; *cerebral malaria* by antimalarial drug therapy.

CHAPTER

23

EPILEPSY AND ANTIEPILEPTIC DRUGS

TYPES, RECENT ADVANCES, DRUG THERAPY AND LIMITATIONS

[The syndrome of cerebral disorders, collectively known as *epilepsy* from prechristian era and comprising of grandmal, petitmal, psychomotor and focal seizures, have all through defied proper treatment and the knowledge about their pathogenesis, is still incomplete. It is a condition of paroxysmal cerebral dysrhythmia with abnormal EEG discharges, emanating from *seizure foci* in the brain, which are nothing but pathologically altered or normal neurones firing excessively the spread of discharges not being controlled by the normal inhibitory mechanisms. The alarming acute convulsive episode of grandmal seizures, the chronicity of the course and the mental and hereditary changes produced in the afflicted patients, had all contributed to the horror associated with this disease in the lay people. In spite of this, no drug was known for this condition till bromides were discovered in 1857, barbiturates in 1912, diphenylhydantoin in 1938 and trimethadione, mysoline, phenurone and others thereafter. None of these drugs can be considered to be highly specific and their toxicity, on prolonged use, as required in this disease, is a deterrent. However, by judicious planning of treatment, in proper combinations,—(a) phenobarbitone, dilantin, mysoline, mesantoin and acetazolamide in *grandmal epilepsy*, (b) tridione, ethosuxamide and acetazolamide in *petitmal epilepsy*, (c) paraldehyde, dilantin, phenobarbitone, tridione in the refractive forms of *status epilepticus* and finally (d) dilantin, mesantoin and phenacemide in *psychomotor seizures*, improvement occurs in 70-80% cases and these miserable children and adults can often carry out an active profession for their living.

Several useful *techniques*—metrazol seizure, electroconvulsion with or without hydration of the animals, *audiogenic seizures* and *EEG studies*, have been evolved for the screening of antiepileptic drugs. Though these techniques are not yet perfect, the way progress is being made in the last few decades, it can be reasonably hoped that even more specific drugs will be forthcoming in future for this terrible disease, which in despair, was once believed to be due to the possession of these miserable creatures, by evil spirits and demoniacal forces.]

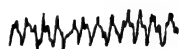
General Considerations. A group of cerebral disorders, collectively known as epilepsy, are time-old syndromes, known from the days of Indian and Greek Medicines. Hippocrates and Paracelsus knew about them and there are records of christian miracles curing this disorder. It was then believed that these patients were possessed of

Plate XXI

E. E. G. PATTERNS IN EPILEPSIES AND STRUCTURE OF ANTIEPILEPTIC DRUGS

GRAND-MAL SEIZURE

HIGH-VOLTAGE FAST WAVES



PETIT-MAL SEIZURE

FAST WAVE AND SPKRE



PETIT-MAL VARIANT

SLOW WAVE AND SPKRE

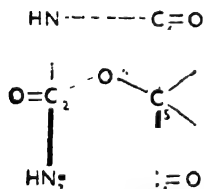


PSYCHOMOTOR ATTACK

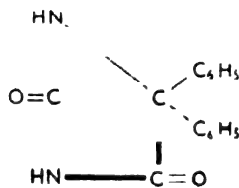
HIGH VOLTAGE SQUARE AND SINE-PERIODIC WAVES



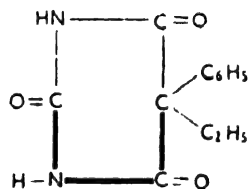
Fig. 57. Electroencephalographic patterns in different types of epilepsies.



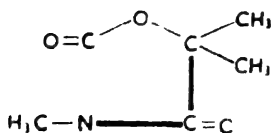
BASIC NUCLEUS



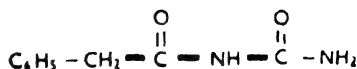
DILANTIN



PHENOBARBITONE



TRIDIONE



PHENURONE

Fig. 58. Chemical structure of important anticonvulsants.

demoniacal spirits and were therefore greatly tortured. In spite of all this, our knowledge of this disease and its treatment, only started in the middle of the last century when Locock first proved the efficacy of bromides in this disease. After this, there was no progress in therapy till to the discovery of phenobarbitone in the earlier part of this century. After the discovery of hydantoin derivatives in 1938, a large number of antiepileptics have been synthesised. The race still continues as an ideal drug has yet to be found out.

There are several types of epilepsy. Where unqualified, it refers to grandmal epilepsy which is the most common one amongst them. It is a condition of paroxysmal cerebral dysrhythmia with abnormal E.E.G. discharges, varying degrees of loss of consciousness and enhanced bodily movements, going up to violent convulsive seizures. It has an inexorably chronic course leading to varying degrees of mental changes.

Stimulation of grey matter normally produces an equal amount of stimulation and inhibition. When the above ratio exceeds the unity and the inhibitory mechanism does not fully work, generalised convulsions, as in grandmal epilepsy, occur. An attack usually starts at one point in the cortex, known as epileptogenic focus and spreads to other parts. The seizure focus may be a collection of pathological neurones or normal neurones firing excessively under stress or it may be due to altered bioelectro-chemical environment, facilitating the spread. The chronicity of the course, its greater incidence in younger age group, hereditary traits in the ailment, mental abnormalities of a functional nature, produced by it and the special F.E.G. patterns, as revealed by elaborate electro encephalographic studies of recent years, are very characteristic of this intricate disease.

TYPES OF EPILEPSY

GRANDMAL SEIZURES	Initial aura, consisting of vague premonitory symptoms of dizziness or headache, followed by sudden loss of consciousness, tonic and then clonic convulsions and post-seizure automatism, confusion and micturition.
PETITMAL SEIZURES (PYKNOEPILEPSY)	No aura but transient clouding of the consciousness, staring expression, blinking and minor movements of head and extremities. It is frequent at childhood and often disappears at adolescence.
PSYCHOMOTOR SEIZURES	Most common in adults and easily confused with petitmal but the episodes are of longer duration and consist of a trance-like state, stereotyped purposeful movements—lips smacking, disrobing etc. Patients become amnesic for a short while after the attack and have a psychotic background.

FOCAL SEIZURES Always acquired and indicative of organic brain disease. Motor, sensory or combined phenomena clinch the site of origin. The seizure progresses from one part of the body to another. The typical example is the Jacksonian type.

Physio-Pathological Considerations. The following factors have been implicated but not finally established in the causation of idiopathic epilepsy: (i) Deficiency in the levels of acetylcholine storage in the epileptic brain. Anticonvulsants are known to cause a rise in the levels of brain acetylcholine. (ii) Deficiency of gamma-amino-butyric acid (GABA), a substance believed to have an inhibitory role in the C.N.S. This has been substantiated by the fact that pyridoxine deficiency is known to produce reduction in brain GABA content, accompanied with convulsions. However, other drugs, which also lower GABA content of brain, do not necessarily produce convulsions. (iii) Alterations in the fluid and electrolyte balance of brain cells increase or decrease the susceptibility to convulsions e.g. hydration of brain and hyponatraemia result in increased predisposition to convulsions. (iv) Some alteration in brain cells similar to those seen in cardiac arrhythmia may be the cause of epilepsy. This is proved by the fact that antiepileptic drugs are sometimes effective in cardiac arrhythmia and vice versa.

E.E.G. Patterns. (Plate-XXI; Fig. 57). In grandmal, there are characteristic fast spike activity (15-40 per second); in petitmal, a more characteristic pattern of slow spikes alternating with rounded waves and in psychomotor epilepsy, less typical changes, usually 4 cycles per second and square waves, are seen over the temporal region.

CLASSIFICATION OF ANTIEPILEPTIC DRUGS

Barbituric acid derivatives	Phenobarbitone, mephobarbitone, metharbitone
Hydantoin derivatives	Diphenyl hydantoin (dilantin), mesantoin, thiantoin, peganone
Oxazolidine derivatives	Trimethadione (tridione), paramethadione (paradione)
Pyrimidone derivatives	Mysoline
Succinimide derivatives	Milontin, ethosuximide (celontin)
Broad spectrum phenyl acetyl urea derivatives	Phenecemide (phenurone)
Miscellaneous drugs	Diamox, bromides and glutamic acid

Chemistry. The structures of anticonvulsant drugs are shown in Plate XXI, Fig. 58. As will be seen, there is a common denominator C-C-N-C represented by bold line in all the groups of antiepileptic drugs. Dash line denotes barbiturate nucleus (phenobarbitone). Dotted line hydantoin nucleus (dilantin and mesantoin). Thin solid line incorporating oxygen represents oxazolidine nucleus (tridione and paraldione). Opening of the hydantoin nucleus between (1) and (5) positions yields the corresponding acetyl urea (phenurone).

Methods of Study. These are both experimental and clinical evaluations by elaborate tests. Though the therapeutic value of antiepileptic drugs is finally established by clinical trials, experimental screening in laboratory animals gives an idea about their prospective value and toxicity. These studies are generally carried out in smaller animals like mice or rats and the procedures adopted for inducing convulsions are either by chemical or electrical shocks.

Metrazol convulsions—these are induced by subcutaneous injection of a 5% solution of the drug in doses of 70 mg/kg. The antiepileptic drugs elevate the threshold to the drug induced convulsions and the therapeutic index is assessed by the dose of the antiepileptic drug that raises convulsive threshold and the dose which produces sedation. Drugs which are highly effective against drug induced convulsion are found to be of value in petitmal epilepsy, as seen with tridione.

Electroconvulsions—are induced by the application of electrodes on the eyes or ears of rats or mice and alternating current or interrupted direct current is applied for a short duration. The convulsion, thus produced, consists of a short initial tonic phase followed by clonic movements. Drugs modifying the pattern of convulsions, abolishing the tonic extensor phase without lowering the threshold, are useful in grandmal epilepsy as in the case of dilantin sodium. Drugs acting in petitmal epilepsy are able to increase the threshold to electroshock as well.

In addition to the above two major procedures, *audiogenic seizure* can be produced in sensitive mice by stimulation with high frequency sound waves. Production of electroconvulsions can be facilitated by *hydrating* the animals by intraperitoneal injection of hypotonic glucose solution. Psychomotor epilepsy can be produced in animals by the administration of slow unidirectional shocks in the temporal region. The protective effects of appropriate drugs can be studied on the above experimentally produced conditions to get an idea about the pharmacological actions of the drugs.

After the pharmacological studies are over, a final *clinical assessment*

of the compounds is made, as per methods detailed in chapter 6, after their toxicity studies have been carefully carried out.

All these methods no doubt, are helpful in the screening of new antiepileptic drugs. It should not, however, be forgotten that the convulsions produced by the above methods are not identical with the convulsions produced in the natural diseases occurring in the human beings because the mechanism of their production is different. Hence these methods are, at best, only qualitative guides.

Based on these observations it has been postulated that the anti-epileptic drugs produce their action probably by: (a) suppression of the abnormal electrical activity of the 'ectopic seizure focus'. In this case, the drug is not only able to check convulsions but also correct the abnormal electroencephalographic pattern of the brain. (b) elevation of the threshold of excitability of the normal brain, thereby preventing the spread of discharges from the ectopic focus and resulting in the abolition of convulsions without correction of the abnormal electroencephalogram. (c) correction of the biochemical abnormalities of the pathologically altered brain cells. However, none of these convey the complete picture of the disease and the action of individual drugs in the different types of epilepsy, and our knowledge of disease is still inadequate.

BARBITURATES

Though these have been studied in the previous chapter, a brief reference of the anticonvulsant barbiturates is warranted.

Phenobarbitone or luminal was discovered by Hauptman in 1912, and still much used because of its cheapness and efficacy. Sedation caused by the drug is a drawback and may require amphetamine for circumvention. When the drug is withdrawn suddenly, seizure may occur with increased frequency. The drug is indicated in grandmal and focal epilepsy but may aggravate psychomotor and petitmal epilepsy, particularly in children. The usual adult dose is 100 mg. twice or thrice a day.

Mephobarbital is less sedative, less potent and costlier. *Dose*: 400-600 mg/day and metharbital, which is the oldest and the longest acting amongst the barbiturates, may be tried in refractory cases in doses of 100 mg. twice or thrice a day.

DIPHENYLHYDANTOIN

Also known as dilantin or phenytoin, this derivative of glycolylurea very much resembles barbiturates and nirvanol (a sedative) and was

introduced by Meritt and Putnam in 1938, as a specific drug for epilepsy. This was long after the barbiturates and bromides had been in use for the condition. It is a white crystalline powder, the sodium salt of which is soluble in water and alcohol. The solution is highly alkaline. It is available as capsules and ampoules. *Dose*: 0.3–0.9 gm.

Metabolism. It is satisfactorily absorbed from the G.I. tract but the action is somewhat slower in onset than the barbiturates. The duration of action of the drug is longer, because of firm binding of the drug to the nervous tissue. After 48 hours, only 6% of the drug remains in the body. Liver is the main organ for detoxification in which the two phenyl groups of the drug are oxidised in stages resulting in the formation of an inert derivative.

Actions. (a) Unlike barbiturates, the drug selectively depresses the motor cortex without much effect on the sensory or any other part of the brain.

(b) It is an effective antagonist of metrazol but not of strychnine and cocaine convulsions.

(c) It elevates electroshock convulsive threshold after the same has been lowered by sodium depletion.

Toxicity. (a) swelling of gums responding to antihistaminics. (b) gastric distress, (c) dizziness, (d) dermatitis.

Uses. (a) Principally, grandmal epilepsy and also status epilepticus. Complete relief in 58% and amelioration in 27% or more cases. Equally effective in focal cortical seizures and some action on the psychomotor type also. (b) Occasionally used in (i) Sydenham's chorea, (ii) delirium tremens, (iii) Parkinsonism, (iv) migraine, and (v) in violent psychotic patients.

THIANTOIN SODIUM

Another hydantoin derivative with a sulphur containing thianyl, is more effective in raising the convulsive threshold and is also less toxic. Given in doses of 0.13 gm. caps./2-3 caps/a day→3 caps/3-4 times a day. Combined with tridione, it can be used in petitmal epilepsy also, with satisfactory results.

MESANTOIN

Methyl-phenyl-ethyl hydantoin or mephexytoin, is 12 times more effective than dilantin but produces some hypnosis in large doses.

Dose: Tab. of 0.05 G—increased every week by 0.05 till a dose of 0.3 G is reached.

Toxicity. (a) liver damage, (b) blood changes, (c) skin rashes.

Uses. Both grandmal and petitmal epilepsy. A more dangerous drug which also produces tolerance on prolonged use.

ETHOTOIN

Also known as Peganon, is another hydantoin derivative, less toxic and less effective in grandmal epilepsy. Daily dose—2-3 gm. and has been tried in psychomotor epilepsy also. It is not a very good drug and has been withdrawn.

MYSOLINE

A pyrimidine derivative, insoluble powder. **Dose**—tabs. of 0.25 gm. — $\frac{1}{2}$ tab/day—to a maximum of 7 tabs/day.

Metabolism. It is readily absorbed from the G.I. tract, maximum action in 6-8 hours, 60-80% excreted in urine; half metabolised and half unchanged. It is present in urine in the form of nirvarol.

Actions. Threshold and pattern of chemically or electrically induced convulsions are modified.

Side Effects. Irritability, vertigo, G.I. upset, drowsiness, ataxia and skin rashes.

Uses. Particularly valuable in *grandmal* and *focal seizures*, but is also used in *petitmal* and *psychomotor seizures*, when given combined with dilantin or tridione. The main advantage is the 'wide safety margin'.

ACETAZOLAMIDE

Also known as 'diamox', is an inhibitor of carbonic anhydrase, which alters the pH of blood to the acidic side. Cases of grandmal, petitmal and psychomotor epilepsies, resistant to other forms of treatment, respond to diamox sometimes. It is given in a dose of 0.5 gm. QDS., but its efficacy wanes after 2-3 months. Combination with other drugs gives better results.

TRIDIONE (trimethadione)

An oxazolidine derivative, white, crystalline, powder of balsamic odour; Sol. 1:20. Caps. of 0.3 gms—2 gm/day in 3-6 doses.

Actions (a) The drug restores the slow spike pattern of petitmal to normality and also produces mild sedation and analgesia like aspirin. (b) It antagonises metrazol convulsions and raises electroshock threshold.

Toxicity. Gastric distress, dizziness and skin rashes and rarely angranulocytosis, aplastic anaemia, purpura, nephrosis and hepatitis. It also produces a peculiar "*glare phenomenon*"—as if every bright object is covered with snow.

Uses. A drug of choice for petitmal epilepsy and very little effective in grandmal seizures.

PARADIONE

It is also an oxazolidine derivative. An oily liquid and slightly soluble in alcohol. In action and use, tridione and paradione are very similar but the latter is less toxic and effective even in patients, resistant to tridione. Dosage schedule is the same as for tridione.

PHENSUXIMIDE

Also known as milontoin, it is an effective compound, particularly in petitmal epilepsy. It is used in doses of 3-4 gm., divided doses per day. Its common side-effects are—nausea, vomiting and dizziness.

BROAD SPECTRUM ANTIEPILEPTICS

There are a few straight chain compounds, recently discovered which block polysynaptic pathways of cerebro-spinal axis and modify electroshock and metrazol seizures. They possess wider spectrum and may be useful in different types of seizures. *Atrolactamid* and *Phenocemide*—are the important members. The first is not available for clinical use.

Phenecemide—or phenurone is a phenylacetylurea compound; creamy—white powder, sparingly soluble and used in a dose of 0.5 gm. tablet/5 times/day.

It is readily absorbed, degraded in liver and quickly excreted in urine. It effectively raises the electroshock threshold and antagonises metrazol

seizures. It is a drug of potency and toxicity as aptly expressed by the term '*Triple Threat*', i.e. efficacy in grandmal, petitmal and psychomotor epilepsies and toxicity on psyche, liver and bone marrow.

It is thus a difficult but useful drug to be handled with caution where other drugs fail. The gastrointestinal distress, fever and anorexia need large doses of Vitamin B Complex. Aplastic anaemia, peptic damage, toxic psychosis and personality changes occur in 20% cases.

GLUTAMIC ACID

This is the only amino acid, known to be metabolised by brain slices to glutamine under laboratory conditions, decreasing the concentration of free ammonia in the tissues. On this basis, it has been used in cases of epilepsy and in mentally deficient children. The recommended dose is 4-8 gm/daily, in divided doses. Real efficacy in therapeutics, is doubtful.

Actions Analysed. Most of the known drugs are believed to modify chemical and electroshock seizures and therefore, it is not possible to differentiate them on this account.

(a) *Dilantin*. Limits the development of maximal seizures and reduces the spread of E.E.G. discharges. The characteristic tonic phase of supra-maximal stimulation is abolished, resulting in the exaggeration of the clonic phase. It is less effective than tridione in raising the electro-seizure threshold and in the spinal phase, barbiturates are more effective in stabilising the hyperexcitability of sodium influx.

(b) *Mysoline*—seems to be more selective in modifying electroshock seizures than others.

(c) *Phenurone*—with its triple threats, abolishes the tonic phase of maximal electroshock.

(d) *Tridione*—elevates the threshold for the minimal clonic and psychomotor electroshock seizures and in larger doses the maximal tonic-clonic seizures also. Unlike phenobarbitone, it does not raise the resting threshold for synaptic excitation but intensifies post-transmission depression, in a manner, opposite to and competitive with metrazol. It is an antifacilitator but not blocker of excitatory synapses. Its action within the thalamus accounts for its role in petitmal epilepsy. It is particularly effective in reducing the amplitude factor of the cortico-thalamic loop, without impairing other ongoing functions in this region. This also explains why barbiturates are ineffective in petitmal epilepsy.

(e) Drugs like tridione have been found to protect patients against petitmal and prevent low characteristics electroencephalographic

changes of the disease. It may be inferred that tridione acts directly on the ectopic focus. Dilantin, on the other hand, is highly effective against grandmal type of convulsion but does not prevent the E.E.G. evidence of the disease. Dilantin thus, appears to act on the normal brain cells raising their threshold and not on the ectopic focus.

(f) Biochemical basis of antiepileptic action has been suggested by inhibition of carbonic anhydrase activity of the brain, alterations in acid-base and electrolyte balance, modification of the brain levels of the local hormones like acetylcholine and GABA, as well as the hormones of adrenal medulla. But as most of the major antiepileptic drugs, used clinically, possess these actions, it is unlikely that biochemical and hormonal factors play any role in their therapeutic value.

THERAPEUTIC ABSTRACT

<i>Drugs</i>	<i>Relative Clinical Efficacy</i>			<i>Dose</i>	<i>Side effects</i>
	<i>Grand-mal</i>	<i>Psycho-motor</i>	<i>Petitmal</i>		
Phenobarbitone	++++	0	+	Below 2 yrs—15 mg. tds. 2—6 yrs—30 mg. „ 6—10 yrs—60 mg. „	Skin rashes, drowsiness, macrocytic anaemia.
Dilantin	++++	++++	0 or—	Below 4 yrs—30 mg. tds Above 6 yrs—100 mg „	Gum hypertrophy, blood dyscrasia, skin rashes.
Tridione	+	+	++++	Below 4 yrs—0.15 G. tds.	Glare phenomenon, sore throat, hepatorenal damage, anaemia.
Phenurone	+	++++	+	Child — 0.25 G. tds. Adult — 2.5 G./day	Hepatorenal damage, blood dyscrasia, G. I. distress.
Bromides	++	0	0 or—	Adult — 0.6-1.3 gm. qds.	Drowsiness, confusion, skin rashes.
Mesantoin	++++	++++	0 or—	Adult — 0.1 G. qds.	Skin rashes, blood dyscrasias.
Melontin	—	—	++	Adult — 3-4 G./day	Nausea, vomiting and dizziness

THERAPEUTIC CONSIDERATIONS

For obvious reasons, treatment of epilepsy presents four major difficulties referring to the (a) disease, (b) drug, (c) patient and (d) doctor.

It has been seen that in spite of all advances, very little is known about the exact pathogenesis of epilepsy. The drugs used are either selective or non-selective depressants, often toxic and have to be used for several years. They have therefore to be used cautiously and withheld or changed on the appearance of the slightest manifestation of toxicity. These may be difficult to be found out, because, often the patients are small children and the parents not sufficiently observant. The doctor has to plan his line of treatment carefully and judiciously, remaining vigilant for the assessment of the efficacy of therapy and follow up the patient long enough for ascertaining the rate of cure or amelioration. The withdrawal of drug or a change to another is also not free from certain hazards. In spite of all these, with the drugs, at present available, much ground has been covered and with judicious therapeutic measures, the prospect of cure and amelioration has risen to over 80 %, with the proviso that the treatment is appropriately designed after making an accurate diagnosis and eliminating other causes like brain tumour, etc. Regular check up of systemic toxicity by laboratory investigations and other studies—urine, blood, liver function tests etc. are very essential. The 'demon' of bygone days, under these conditions, is well under control and a predominantly large section of these miserable patients, can lead a useful life without causing any misery to their relations and the State.

Plan of Treatment. Though this will depend upon the diagnosis of the exact type of disease but the essential principles of therapy and precautions would remain practically the same for all.

Grandmal epilepsy. Of the two major drugs, dilantin and barbiturates, though dilantin is endowed with more selective action on the motor cortex, there is some difference in views about the drug with which treatment is to be started. While one school advocates that dilantin should be given at the commencement of treatment and phenobarbitone to be added to it later on, others prefer to do the other way round claiming better results. Whatever may it be, the correct approach would be in designing that form of treatment which would effectively abolish cerebral dysrhythmia, without much untoward side-effects.

A practical programme, based on the safety and efficacy, seems to be as follows: (a) to start the treatment with *phenobarbitone* 30-120 mg.

tds., gradually increasing the dose till the seizures are fully controlled and then cautiously reducing it to a maintenance dose. All this time, the efficacy of the treatment should be fully assessed. (b) If ineffective or not fully effective, *dilantin* should be added, to give the benefit of combined therapy, which is sometimes better than a single drug therapy. (c) Even then, if the seizures are not fully controlled, the exact type of epilepsy should be critically reassessed and the line of treatment reoriented. (d) Resistant grandmal types may be given *mysoline*, followed by *mesantoin*, in combination with *acetazolamide*, in dosage schedules prescribed and then gradually increased. Overall results are about 60% controlled and about 20% improved.

Petitmal epilepsy. Though tridione—0.3 gm/tds. or qds. is mostly used, the newer drug ethosuximide is less toxic and more effective, in a dose of 250 mg. capsules, 4-6 times a day. In the case of failure, milontin or acetazolamide should be tried. Results—73% controlled and 12% improved.

Status epilepticus. In *grandmal status*, paraldehyde 5—10 ml. I.M. or phenobarbitone 0.2 gm. I.V. or dilantin sodium 0.3 gm. I.V. is administered routinely. *Petitmal status*, which represents only 20% of all the cases, is treated with tridione given in a dose of (1—5) gm. generally. Other drugs are indicated if the above fail.

Psychomotor epilepsy. These complex psychic seizures, related to foci in the anterior temporal lobe, are much less amenable to anticonvulsant therapy. Dilantin is often used. Phenobarbitone and bromides should not be used. Mesantoin may be added and so also phenoceamide, if necessary. Only 20% of the cases can be controlled and another 40% improved.

CHAPTER

24

PHARMACOLOGY OF VOMITING

PHYSIOLOGICAL CONSIDERATIONS. VOMITING CENTRE AND C.T.Z. IN THE MECHANISM OF MOTION AND OTHER SICKNESSES. NATURE OF ACTION AND THERAPEUTIC STATUS OF EMETICS AND ANTIEMETIC DRUGS

[Many drugs given orally, or some even otherwise — cardiac glycosides, salicylates, emetine and quinine, produce nausea and vomiting as undesirable side-effects, while others, by their central or peripheral mechanism of action, produce the same as toxic manifestations. *Emetics* like copper and zinc sulphates mercuric perchloride and apomorphine are sometimes used as emergency measures for evacuating the contents of stomach in cases of poisoning. The *antiemetics*, comprising of a larger number of old and new drugs, are used for combating vomiting due to drugs, pregnancy, radiation and motion sicknesses.

Mechanisms of vomiting are complex and diverse, implicating the vomiting center, as well as, chemoreceptor trigger zone situated in the medulla, near each other. Irritants like copper and zinc sulphates stimulate the vomiting centre through the G. I. tract *reflexly* and produce vomiting. Similar effects on the centre are also producible by impulses from higher visual and psychic centres. Veratrum alkaloids produce vomiting by the stimulation of nodose ganglion of the vagus nerve. Excessive motion causes vomiting due to a chain stimulation of labyrinth, 8th nerve, cerebellum, C.T.Z. and finally the vomiting centre. Emetics like apomorphine, morphine, cardiac glycosides, quinine and emetine produce vomiting through the CTZ, while ipecac and tartar emetic produce vomiting as peripheral effect, whereas copper sulphate acts peripherally, as well as, on the vomiting centre.

The important *antiemetics* belong to several groups: (a) *Anticholinergic*—atropine, and hyoscine, (b) *Sedatives* — bromides and chloroform, (c) *Antihistaminics* — dramamine, avomine and cyclizine and (d) *Miscellaneous drugs* — dilute hydrocyanic acid, aqua chloroform, and sodium bicarbonate.

For *ordinary vomiting*: gastric lavage, use of gastric sedatives, sodium bicarbonate, bismuth subnitrate, replacement of fluid and electrolyte loss may often suffice while for *motion sickness*, dramamine and cyclizine are indicated. For *vomiting of pregnancy*, cyclizine, pyridoxine and other B complex vitamins, insulin and glucose are prescribed. The above, along with adequate rest to the stomach by withholding of solid food but permitting sipping of water and some nourishing fluids may meet with the requirements of treatment.]

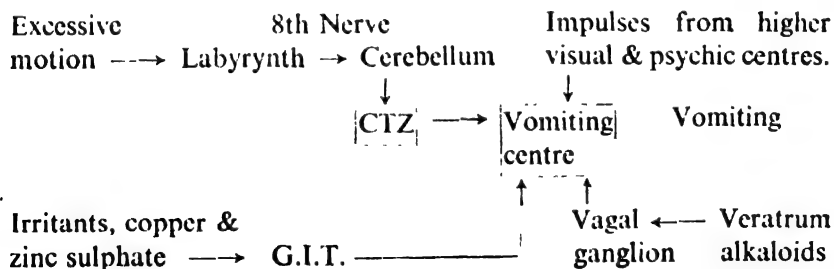
Many drugs like broad spectrum antibiotics, morphine, nitrogen mustard, salicylates, quinine and glycosides cause nausea and vomit-

ing as undesirable side effects even when used in therapeutic doses, while others produce emesis as a manifestation of their toxicity. In this chapter, those drugs which are used intentionally to induce vomiting in an emergency for emptying the stomach, with or without the simultaneous use of a stomach tube, will be discussed. Similarly, antiemetics which are used to combat nausea and vomiting due to drugs, pregnancy, radiation sickness and other causes, thus constituting an important chapter in therapeutics, will also be studied.

Physiological Considerations: Vomiting refers to the forceful expulsion of the gastric contents through the mouth, while nausea is a complex phenomenon, usually referring to a feeling of sickness.

Vomiting can be initiated from almost any site of the body. Transmission of afferent impulses to the vomiting centre occurs in vagal or sympathetic nerves or both, while efferent impulses, travel in the nerves supplying the muscles of the diaphragm and abdomen. Before vomiting takes place, there is increased salivation and after a deep breath, the glottis closes, the cardiac orifice of the stomach opens, the musculature of the stomach and the oesophagus relax and the muscles of the diaphragm and abdomen contract strongly, compressing the stomach and forcing out its contents.

Centres. These comprise the vomiting centres as well as the chemoreceptor trigger zone (C.T.Z.). The vomiting centre lies in the lateral reticular formation of the medulla oblongata in the fascicularis solitarius, while CTZ lies close to the vagal nuclei and is physiologically separate from the former, although anatomically the two zones are very close. Both of them serve as sites of action of drugs which cause vomiting —



Motion sickness: The normal regulation of posture is effected by the smooth functioning of the vestibular apparatus, cerebellum and the cortex. Changes in the body posture stimulate the sensory cells of

the vestibular apparatus, which then sends impulses through the 8th nerve to the cerebellum and there, as a result of coordinated nervous activity, the motor system is made to work in such a manner that the abnormal posture is corrected. The vestibular apparatus through the cerebellum is connected to the C.T.Z. which, in turn, has connection with the vomiting centre. Excessive stimulation of the vestibular apparatus, particularly due to the jolting and jerking, which frequently happens while travelling in a ship, airplane or bus causes reflex stimulation of the vomiting centre. Along with this, the visual and psychic stimuli also help and thus in susceptible persons, vomiting associated with cold sweating, salivation, headache and a feeling of severe prostration occurs. All these together constitute the syndrome of 'motion sickness'.

The above mentioned path of the reflex has been confirmed experimentally and it has been found out that up and down movements are greatly responsible for this sickness and the patients feel better on lying down. Cutting of the 8th nerve, removal of certain parts of the cerebellum, containing the nuclei of the vestibular apparatus, like the nodules and uvula and destruction of the C.T.Z. abolish this vomiting.

From these experiments, it is now established that vestibular stimulation especially of the utricular macula, is the most important factor in the causation of motion sickness. The efferent nerve pathways run via the 8th nerve to the areas lying in the cerebellum and medulla oblongata, which receive and integrate these impulses.

The sequence of events in the vomiting of motion sickness is as follows:

Stimulation of the utricular macula by the movements of the otoliths → impulses along 8th nerve → cerebellum (nodulus & uvula) → C.T.Z. → vomiting centre → emesis.

Evaluation: (a) Steriotaxic technique—induction of vomiting by selective stimulation of the vomiting centre and for the C.T.Z. and study of effects of antiemetic drugs.

(b) Effect of emetics after destruction of different brain areas to determine the site of action and nervous pathways.

(c) Effect of emetics on drug induced emesis in animals.

Of these various emetics, copper and zinc sulphate are sometimes used in poisoning cases, as they act quickly and produce little nausea and after effects. Ipecac and tartar emetic which act reflexly, and apomorphine centrally, are little used in therapeutics these days. The peripherally active emetics cause vomiting by acting upon the stomach and upper duodenum. They must be given with a fairly large volume

CLASSIFICATION

Emetics	Antiemetics
Central —apomorphine, morphine, cardiac glycosides, veratrum, quinine, nicotine.	Anticholinergic —atropine, hyoscine. Antihistaminics —dramamine, benadryl, avomine, promethazine, chlorpromazine, cyclizine, chlorcyclizine, meclizine.
Peripheral —Copper sulphate, zinc sulphate, ipecac, tartar emetic, mustard, common salt.	C.N.S. depressants — bromides, chloral hydrate, chlorbutanol, barbiturates. Miscellaneous — dilute hydrocyanic acid, aqua chloroformi, glucose, mag sulph.

of fluid so that they can reach the pylorus and upper duodenum quickly. They irritate G.I. mucosa, stimulate afferent nerve endings, which impulse pass through the C.T.Z. and reach the vomiting centre. If the first is destroyed, vomiting does not occur.

EMETICS

Apomorphine: A derivative of morphine produced by the action of strong acid. *Dose*—2-8 mg. S.C. Its emetic action is produced centrally through the stimulation of the C.T.Z. within 5-10 mins. There is however a series of vomiting spells which lasts for 1-2 hours.

Cupric Sulphate: 0.3 gm dissolved in 100 ml. of water. If vomiting does not occur after the first dose, a second dose may be given after 15-20 mins. *Zinc sulphate* 0.6 to 2 gm dissolved in 200 ml. of water may also be given and repeated after 15 mins. interval, if necessary. *Mercuric chloride* or hydrarg perchlor; also acts as an emetic in a similar manner.

Ipecac: Its emetic action is due to the local effect of the two alkaloids—emetine and cephaline. When absorbed, they can also exert some central emetic action. *Dose*—powder-1-2 gm. Syrup 8 ml. Tinct. 15-30 ml. *Antimony sodium and potassium tartrates*—30-60 mg. is not used because of its toxicity.

ANTI-EMETICS

Belladonna alkaloids: *Atropine* and *hyoscine* are both potent motion sickness agents. Their action seems to be mediated through their *anticholinergic* effects. It is believed that antihistaminics also show

their effectiveness, at least partly from their atropine like properties. Many of the symptoms of motion sickness resemble to be of parasympathomimetic nature. However, the participation of acetylcholine in this mechanism has not been substantiated. Synthetic atropine like compounds are devoid of this action.

Of the alkaloids of belladonna, *hyoscine hydrobromide*—0.75 mg. is the best and no other compound has shown any superior ability to prevent all forms of motion sickness. Atropine is used in a dose of 1 mg. one hour before the journey. Both of them produce their usual side effects which are inconvenient to the patient. Their action lasts for about 6 hours. Hyoscine protects against apomorphine vomiting and is used also in the treatment of vomiting of pregnancy and irradiation sickness.

Antihistaminics: A large number of antihistaminics possess potent antimotion sickness properties. Their exact mechanism of action is far from clear, but it is interesting to note that all of them possess some degree of enticlolinergeric action besides being sedatives also. They are the most frequently used these days both in motion sickness and in other types of vomiting.

Cyclizine: an effective motion sickness preventive and is also employed in the vomiting of pregnancy and vertigo. Its antihistaminic potency is equal to that of benadryl. *Dose*—50 mg. t.d.s. It may produce drowsiness, dry mouth and blurred vision.

Meclizine: another histaminic which is effective in sea and air sicknesses. A single dose of 50 mg. provides protection for 24 hours or longer.

Diphenhydramine (benadryl): It is an effective antimotion sickness drug, but causes drowsiness and sedation. *Dose*—100 mg.

Promethazine and avomine: gives protection against sea and air sicknesses. The action of a single dose of 50 mg. lasts for 20 hours. They may cause sedation drowsiness, dry mouth and blurred vision.

Chlorpromazine: a potent antiemetic, but of little value in the prevention or treatment of motion sickness. It is invaluable in the vomiting due to drugs, pregnancy and uraemia.

Other Drugs: *Barbiturates* are used to prevent or treat motion sickness and their activity is probably due to their sedative and hypnotic effects. *Acid hydrocyanic dil.* 2-5 mg. is also a gastric sedative. It is used in cases of vomiting with marked G.I. irritation. *Aqua chloroformi* 15-30 ml is another gastric sedative, occasionally used in vomiting, alone or as a vehicle for other drugs in a mixture.

MANAGEMENT OF VOMITING

This will depend on the type, as well as etiology of vomiting. If it is the safety valve action of the stomach to reject unwanted contents, a few ejections should be permitted.

Ordinary Vomiting: This is usually due to ingestion of bad food and irritating substances and the treatment is mostly symptomatic.

Bed rest, abstinence from food but fluids may be given by mouth in small amounts. Sodium bicarbonate—2 gm. or bismuth subnitrate—2 gm in hot water should be prescribed. If the symptoms persist, gastric lavage, sodium bromide or chloral hydrate 1-2 gm/os or rectum, may be given.

In severe cases—(a) Fluid and chloride loss is to be made up by I.V. saline or glucose solution.

(b) Dramamine 50-100 mg or thorazine 25 mg should also be prescribed.

Motion Sickness: The management comprises prophylactic measures, as well as, drug therapy.

Prophylactic: (a) A purgative 12 hours before the journey, (b) High carbohydrate and low fat diet, (c) Lying down in bed, (d) Avoidance of alcoholic drinks or loss of sleep.

Drugs Therapy: Comprises mostly of the use some of the anti-histaminics. *Dramamine* is an effective prophylactic in doses of 100 mg., one hour before commencing the journey, followed by 100 mg/4 hrly. *Cyclizine* (merzine), given in doses of 50 mg t.d.s./o.s., relieves motion sickness at the early stages of dizziness, sweating and nausea.

Vomiting of Pregnancy: This is a serious condition requiring energetic and effective measures of therapy. (a) Cyclizine HCl, 25 mg at bed time. (b) Vitamin B complex or Vitamin B₆ (pyridoxine) and Vitamin C, parenterally. (c) In severe cases, food is to be withheld by mouth and given intrarectally, along with I.V. injection of glucose saline and insulin in small doses. (d) If there is evidence of late toxæmia phase of vomiting, abortion is to be induced.

CHAPTER

25

PHARMACOLOGY OF HABIT FORMING DRUGS ETHANOL AND OPIUM ALKALOIDS

NARCOTIC-HYPNOTIC AND ANALGESIC DRUGS. PROBLEM OF DRUG ADDICTION AND MANAGEMENT.

[Some of the narcotics, while depressing the C.N.S. in a general, as well as, selective manner, produce an irresistible craving, leading to habit formation and addiction. Alcohol, opium, *Cannabis indica* and cocaine belong to this group. Drug addiction is a psychosomatic condition embracing habituation, tolerance and drug dependence which phenomena are psychic, biochemical and physiological, respectively. They produce disturbances in homoeostasis and devastating withdrawal symptoms, which are difficult to manage. Drug addiction is thus a great social danger and with the discovery of newer psychopharmacological agents more drugs are being observed to induce addiction liabilities than in the past in young people with delinquent tendencies.

Of the two important addictive drugs — *alcohol* and *morphine* included in this chapter, *alcohol* is obtained by the fermentation of starch and has been assigned wide pharmacological actions and uses in the past. On *topical application*, it is rebefticent, anhydrotic, counterirritant and antiseptic. *Internally*, it is a C.N.S. depressant, the apparent stimulation caused by it being due to the depression of the higher inhibitory centres. It has uncertain actions on the cardiovascular system in therapeutic doses. Its stomachic and diuretic actions are also insignificant and its food value is controversial, as it supplies calories without building up any reserve. Its acute and chronic toxicities are considerable and its effect on heredity and longevity, and its role as a social danger, cannot be ignored. Excepting brandy, which is used as a stimulant, its therapeutic use is extremely limited but pharmaceutical use, as a solvent is important. For the treatment of chronic alcoholism, disulfuram (antabuse), may be tried.

Opium owes its activity to its large series of alkaloids, of which, the important ones are morphine, codeine and papaverine. Morphine is an analgesic — hypnotic and a respiratory depressant. It is spasmogenic for plain muscles and is a capital drug for relief of visceral pain. The importance of morphine has been reduced to some extent, by *Pethidine*. *Codeine* is a cough sedative and *papaverine* a plain muscle relaxant. *Pethidine* combines the analgesic effect of morphine and the antispasmodic effect of atropine. It has less addiction liabilities and is more frequently used in conditions of myocardial infarction, renal and biliary colic etc., for which morphine used to be used, in the past.

All the untoward effects of morphine and pethidine are effectively reversed by *n-allyl normorphine (nalorphine)*, which acts by *end-organ competition* and is successfully used not only for morphine poisoning but also for neonatal respiratory depression due to morphine, as well as, for *diagnosis of morphine addiction*.]

A number of narcotics act as central nervous system depressant, inhibit higher centres and produce an irresistible craving or 'drug habit'. Some of them like alcohol, possesses hypnotic action along with others, while opium and its alkaloids also produce marked analgesic actions. So far as *cannabis indica* is concerned, it is a hallucinogen and intoxicant, while cocaine is a local anaesthetic and when absorbed in sufficient quantities, provokes worst drug habit.

The other groups of substances,—coffee, tea and tobacco are quite different in their addicting properties, as already discussed earlier.

Alcohol and opium group of alkaloids, along with their derivatives and substitutes, will be discussed in this chapter.

ALCOHOL

The word *alcohol* is derived from the Arabic 'Al' and Hebrew 'Kakahl', meaning *eye wash*. When we go through the psycho-pharmacological effects of the drug, the colouring of vision and judgement in alcoholics and also its therapeutic uses, we realise, how it acts as a real 'eye wash' in every sphere.

Types: There are *two principal types* of alcohol—(a) ethyl and (b) methyl. The unqualified word refers to 'ethyl alcohol'.

Alcohols are all prepared by fermentation of starch. Their properties increase in the homologous series—methanol (CH_3OH), ethanol ($\text{C}_2\text{H}_5\text{OH}$), propanol ($\text{C}_3\text{H}_7\text{OH}$), heptanol ($\text{C}_7\text{H}_{15}\text{OH}$), etc.

Whatever may be the clinical status of alcohol it is an important item in Pharmaceutical chemistry. The Pharmacopoeia owes much to this solvent and our societies, the least.

1. *Ethyl alcohol* : (a) Absolute alcohol — 99.4% (b) Rectified spirit — 95, 70 . . . 45-30%, is meant for internal and laboratory uses.

2. *Methylated spirit* : (alcohol methylatus industrialis): 19 parts of ethyl alcohol and 1 part of wood naphtha. It is very toxic producing retinitis, optic atrophy, cardiac depression, cerebral oedema and death. It is unsuitable for internal use and is used externally only. It is adsorbed and destroyed slowly—about 2/3 in 2 days.

3. *Liquors, wines and beverages* : An important industry and a source of national wealth in certain countries.

(a) During the process of fermentation of starch, grapes and molasses, alcohol is formed to the extent of 95% of ethyl alcohol and the rest 5% as propyl, butyl and amyl alcohol, collectively known as '*fusil oil*' which is the irritating principle for the mucous membrane. It also contains '*furfural*', the toxic substance for liver and other organs.

(b) Ripening of wine removes partially fusil oil and furfurol.

(c) The aldehydes and the esters, present in alcohol, contribute to the flavour and taste. Alcohol percentage is not everything in wines, the other ingredients are also important.

<i>Alcohol %</i>	<i>Types of beverages</i>	<i>Source</i>	<i>Action and uses</i>
47-53	Whisky, brandy, whodka.	Malted cereals, molasses, rice.	Stimulant and used for cold.
15-23	Sherry, port, champagne.	Fortified special wines.	Tonic for convalescence. The last gives eloquence.
5-10	Ordinary wines, cider. Ale, stout, beer.	Grapes, apples, malt.	Appetiser, pleasant drink and diuretic.

Retrospect Analysis: Alcohol is an old friend of humanity and man trying to see the universe in his own image, has made it an old friend of divinity as well. The use of 'someras' from fermented fruits, is described in the Vedas. The word 'whisky' in gaelic means 'water of life'. It may appear that the mendicants who try to see the unseeable and may be the realisable 'God', require a third eye which can be provided by alcohol, by lifting the barriers of psychic inhibition of a normal mind.

Metabolism: Comprising the following:

Absorption: (a) Usually rapid (1-2 hrs); about 20% from the stomach and the rest from the intestine. It is also absorbed through the skin and the lungs. (b) Its absorption is increased in concentrated form and in empty stomach.

Distribution : This is uniform and commences within 5 minutes of ingestion. It passes all the barriers — placenta, blood-brain, etc.

Destruction : (a) About 90% of alcohol is destroyed by oxidation (10 ml/hr) giving 70 calories of energy (Mallanby), chiefly by liver. Glucose and insulin are of value in acute intoxication.

Excretion: About 10% escaping oxidation is excreted through most of the secretions (about 5%) through the lungs. The breath smells alcohol after a drink, about 30% alcohol is excreted in urine out of which, a small quantity is again reabsorbed through the bladder epithelium. The system apparently does not want to get rid of alcohol.

Urine and blood both have practically the same concentration of alcohol. Concentrated alcohol gives higher concentration than the diluted one.

Alcohol content in blood and urine after 27.5 gm.

Time	Alcohol in mg/ml. after 27.5 gm in 1000 ml.				Alcohol in mg/ml. after 27.5 gm in 100 ml.			
	20	40	70	120	20	40	70	120
Blood concentration	0.18	0.24	0.31	0.31	0.29	0.43	0.44	0.37
Urine concentration	0.16	0.30	0.48	0.43	0.29	0.54	0.63	0.50

Miles Table : Showing % of alcohol in blood and different degrees of intoxication.

0.01	clearing of head	0.1	perceptible staggering
0.02	feeling of warmth	0.2	needs help for walking
0.03	mild euphoria	0.3	stupor in certain cases
0.04	lot of energy	0.4	deep anaesthesia
0.05	sitting on the top of the world 'A free man'	0.5-0.8	absolutely fatal

Blood concentration of alcohol is thus highest in 1-2 hours. Thereafter, there is a quick fall in the habituated and slow fall in the abstainers.

Actions: (a) Local and (b) Systemic — both largely exploited.

Local : Due to its affinity for water and rapid evaporation, it produces cooling effects, followed by irritation and also protein precipitation, in high concentrations. It thus acts as a rubefacient, counter-irritant, anhydrotic and antiseptic. It is used in neonatal cases as respiratory stimulant and also in bed sores. 70% alcohol is suitable for cleansing and antiseptic actions.

Systemic : C.N.S. Contrary to the general idea, alcohol is not a stimulant but a depressant through and through. The apparent stimulation is due to the depression of the higher centres, the lower centres thus being let loose.

(a) Abounding confidence, emotivity, impulsive speech, loss of finer grades of discrimination, memory, power of concentration and decreased efficiency in work. (b) Irregularly descending depression of the C.N.S. as with anaesthetics, but not suitable for anaesthesia in view of the narrow margin between the anaesthetic and the lethal concentration.

Alcohol ————— Anaesthesia ————— Death
Ether ————— Anaesthesia ————— Death

C.V. System : It causes uncertain stimulation of the heart and the pulse rate, mild peripheral vasodilatation and in strong doses, marked depression of the C.V. system.

G.I. tract : There is a mild stomachic and carminative action, but at 20% concentration, there is inhibition and at 40% concentration, irritation and hyperaemia, leading to chronic gastritis.

Kidneys: (a) The diuretic action is partly due to the fluid intake also. (b) In habitual drunkards, there is nephritic lesions and also precipitation of gouty attacks.

Liver : A hepatotoxic drug of importance, producing fatty degeneration and cirrhosis (Laennec and other types).

Sexual functions : Shakespeare in Macbeth, beautifully describes the current consensus of opinion—'It provokes and unprovokes, it provokes the desire but takes away the performance.' It is not a true aphrodisiac.

Skeletal muscle : It is not a true stimulant. It produces vasodilatation and decreased fatigue but muscle endurance is definitely decreased.

Food value : This is a controversial issue—

(a) Like C.H. and fat, alcohol supplies energy (7 cal./gm) but produces no reserves like carbohydrate and it is not a tissue builder like protein. (b) Given with food, it spares carbohydrate, protein and fat and has much simpler metabolism than them. (c) Alcohol is not essentially required as a food and is an expensive source of energy.

Intoxication: Acute and chronic.

Acute : Psychic and other effects: soaring imagination, talkativeness, violence, incoordination, passing into a stage of depression, somnolence and death from respiratory failure.

Treatment : (a) stomach wash, (b) black coffee, (c) analeptics ($\text{CO}_2 + \text{O}_2$ mixture), (d) bromides and sodium bicarbonate for after-headache.

Chronic : (a) There are gross mental, gastrointestinal, hepatic and renal changes and also peripheral neuritis from Vit. B₁ deficiency.

(b) Korsakoff's syndrome—with loss of memory for time and space, fine tremors and psychosis, with confusion and emotivity.

(c) Delirium tremens, either after heavy bouts or from abstinence. There is delirium, hallucination and exhaustion.

Treatment : (a) Sympathetic nursing, (b) paraldehyde, (c) thiamine and I.V. glucose.

Heredity and Longevity: This has not been definitely settled.

(a) Miss Durham's interesting work on 18 generations of guinea pigs with alcohol in which no appreciable adverse effects were observed.

However, man and guinea pigs are not comparable. (b) Insanity, mental defects, epilepsy and gout: no definite aggravation has been observed in controlled studies.

Alcohol as a Social Danger: (a) Over 5 crores of people drink in this world. Quite a good number of them drink more, eat less and feed their family still less. Drinking thus is a deplorable evil. (b) People often drink for escaping the nude realities of life and for passing on to the subcortical level of mind. Our moral, economical and ethical standard of society must improve before drinking evil can be completely eliminated.

There is another aspect of the problem which is a scientific one:

(a) Alcohol is a normal constituent of the body of drinkers, abstainers, vegetarians and non-vegetarians. (b) Degradation of C.H. to CO_2 passes through the stages of lactic acid \rightarrow ethyl alcohol \rightarrow acetic aldehyde. (c) Human brain contains 0.0004% and blood 0.004% of alcohol. None can then escape it completely and it is only a question of degree.

Management of Chronic Alcoholism: Sudden or gradual withdrawal in the hospital or nursing home environment, associated with judicious use of stimulants or chlorpromazine type of tranquillisers, sympathetic nursing, psychiatric treatment, correction of mal-adjustments, nourishing food and vitamins, change of environment and society, have been the time old therapeutic measures, with mixed results. Since the discovery of antabuse, this new drug is now used for removing the craving for alcohol in chronic addiction.

Uses: *A. Externally* — as indicated earlier,

- (a) Skin disinfectant (70% strength).
- (b) Relief of headache — caudecologne.
- (c) Sciatica and toothache — Inj. in the nerve sheath.
- (d) Counterirritant, anhydrotic and hardening agent in bed sores.

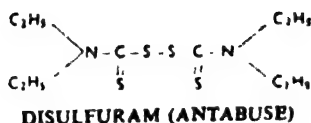
B. Internally

- (a) As a general stimulant after acute illness in the form of tonics containing port or sherry as in 'manola' used after delivery.
- (b) Brandy in cases of fainting.
- (c) Crisis of pneumonia-use discarded now.

Caution : Alcohol should never be prescribed to a weak minded patient.

ANTABUSE

This is a recently discovered synthetic compound which has brought a new approach to the management of chronic alcoholism. Chemically it is a tetraethyl-thiuram disulphide (TETD) and also known as disulphuram, having the following structure.



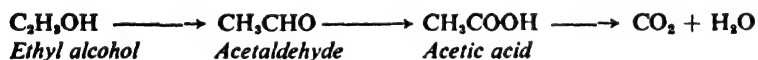
Chemical nature of antabuse

Primarily used as anthelmintic, Jacobsen and Hald (1940), while using the drug on rabbits, tried on themselves after having already taken some cocktail. They immediately developed severe gastrointestinal distress and thus discovered the sensitising property of antabuse vis-a-vis alcohol.

Character : Grey, tasteless powder, soluble in fat solvents and dispensed as 0.5 gm tablets for oral use.

Metabolism : It is rapidly absorbed from the G.I. tract and oxidised in the body. It is excreted in urine as sulphate (50% in 24 hours).

Action : Normally when alcohol is ingested, it is metabolised as under:



Conversion of acetaldehyde to acetic acid is effected by the aldehyde oxidase present in the liver and muscles. This enzymatic action is depressed by antabuse and consequently, the metabolism of alcohol is arrested at the stage of acetaldehyde, which by accumulation, produces the following violent reactions in the alcoholic, under antabuse therapy—

(a) Scarlet face, bull eyes, and bursting headache. (b) Severe gastrointestinal trouble, garlic taste, tachycardia and hypotension. (c) Dizziness, mental confusion, profuse perspiration, and acneform eruptions.

This uncomfortable reaction is produced at a blood concentration of 10-15 mg% of acetyldehyde and lasts for about half an hour. The unpleasant symptoms make the patient abhor drinking and then gradually to give up the habit.

The therapy however, is a violent one and is full of sideeffects—arrhythmia, C.V. collapse and respiratory depression. The after effects last for 3-4 days, after which, the patient is tempted to drink again, unless he continues small doses of disulfuram and also develops will-power.

Method of Use : (a) After one week's abstinence from alcohol, when the patient is in better physical condition, antabuse is given according to the following dosage schedule:

1st day—2 gm; 2nd day—1.5 gm; 3rd day—1 gm; 4th and 5th day—0.75 gm each.

(b) 20 ml. of whisky is given on the 5th day for precipitating the syndrome.

(c) A maintenance dose of 0.25–0.5 gm of antabuse is continued every morning for creating voluntary resistance and will power for abstinence.

Contra-indications: Any serious constitutional disease (a) diabetes (b) cardiac disease, (c) Cirrhosis or nephritis.

OPIUM

Opium and its alkaloids are (a) primarily analgesics (b) also hypnotics and (c) in repeated and habitual doses, narcotics. Until recently opium has been a sheet anchor in our therapeutics. It therefore requires to be studied in some detail.

Historical: History of opiaces is lost almost in the antiquity.

(a) Ebers, in the prechristian era, knew about its anodyne properties and Homer speaking of its somnolent action, said 'whose drinks thereof, no tears flow down the cheeks'.

(b) The drug was known to Theophrastus, Galen, and Paracelsus and Sydenham used 'Laudanum, so frequently, that he was nicknamed as 'Doctor opeatus'

(c) Use of poppy capsules permitted Napoleon to save a part of his defeated army from Egypt.

Opium in Greek, means 'juice'. It is the dried juice of 'Papaver-somniferum' obtained from the unripe capsules by incision (Plate XVII).

The poppy is an annual plant about 2' high. The juice dries off next morning, becomes brownish, is then scraped off, packed with poppy leaves and despatched. It is sticky, bitter and of characteristic odour,

Varieties : 4 important sources:

- | | |
|---------------------------|---|
| (a) Turkey—most important | (b) Persia |
| (c) India | (d) South European countries—
Greece, Belgium and France |

Nearly 1000 tons of opium is used every year all over the world.

Active Principles: Opium acts by virtue of its alkaloids, which represent about 25%. Besides, it also contains meconine, meconic acid and resin representing 75% opium. The important alkaloids belong to 2 distinctive groups:

1. *Phenanthrene group* : Morphine—10%, codeine—0.5% thebaine—0.2%
2. *Benzylisoquinolene group* : Papeverine—1%; narcotine—6%; Narceine—0.3%; Laudanosin-traces.

The *first group* is predominantly analgesic, narcotic, hypnotic and also C.N.S. depressant while the *second group* is predominantly antispasmodic for plain muscle, with little central analgesic, narcotic or C.N.S. depressant effects. Besides these important natural alkaloids, there are a number of derivatives and substitutes which are more often used than the natural alkaloids.

Preparations : Several and much used in the past—(a) Powder containing 10% of morphia (b) Dry extract, (c) Pulv. creta aromatica with opio, (d) Dover's powder, (e) Tinct. opii (Laudanesin), (f) Tinct. opii camphorata (Paregoric) -2-4 ml. and finally, morphine hydrochloride, sulphate tartarate salts—7.5-20 mg.

MORPHINE

It is the principal alkaloid of opium, isolated by Sertürner in 1809, tested upon himself and named after the Greek God 'Morpheus', the god of dreams. All the preparations are standardised in terms of this alkaloid.

Metabolism: (a) *Absorption* : This is adequate from the G.I. tract but still better from the subcutaneous tissues. The action starts almost in 5 mins. It is not absorbed through the skin and m.m., its topical application is without any scientific basis.

(b) From the blood, morphia passes into the tissues, where about 2/3 is broken and about 60-70% is eliminated in faeces and the rest in urine. The kidneys have high threshold for morphine but this is not so far codeine.

(c) Morphia is excreted mostly in free form and liver is the organ for detoxication.

Actions: The principal actions of morphine are on the following three systems:

(a) C.N.S. (b) Respiratory system. (c) G.I. tract. The rest are all unimportant ones.

Central Nervous system : (a) Relief of pain, of visceral and traumatic origin. It is not the best drug for any other type of pain viz. skin, joints or muscle pains. (b) It acts on the sensory cortex and increases the threshold for pain. This relieves anxiety and alarm and the patient goes to sleep. (c) Morphine is also a cortical depressant and hypnotic, but may stimulate non-narcotisable animals like cats and pigs. (d) Respiratory, cough and V.M. medullary centres are all depressed but the vomiting and vagal centres may be stimulated. (e) Reflex spinal centres are usually stimulated. In decerebrate frogs, it produces strychnine like convulsions but in normal frogs, cortical depression may hold the spinal stimulation in abeyance. (f) It causes characteristic pinpoint pupil which is of central origin through the oculomotor nerve.

Respiratory system : (a) It is a depressant of the cough centre and is thus a sedative and soothing drug for irritating cough. The secretions of mucus is decreased. (b) There is mild broncho-dilatation but codeine and papaverine are better in this respect. (c) Ultimately there is depression of the respiratory centre with slow sighing respiration leading towards 'Cheyne-stokes type' (Plate XXIII: Fig. 60).

These effects are due to central depression, asphyxia and cerebral anaemia. The centre loses its normal reactivity to CO_2 changes.

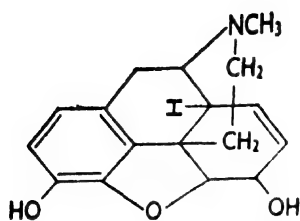
G.I. Tract : (a) Dryness of mouth, diminished secretions and loss of appetite.

(b) Studies with barium meal reveal: (i) increased tone and spasm of the colonic muscles. (ii) decreased peristalsis; constriction of pyloric and ileocaecal sphincters. (iii) delayed exit and abolition of defaecation reflex from the central effect. The net result is constipation.

EFFECT OF MORPHIA ON BARIUM MEAL

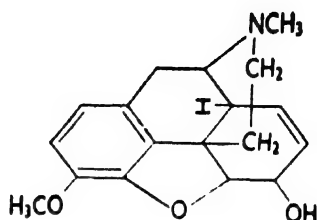
	Normal hrs.	After Morphine hrs.
Small intestine—first appearance	0.4	1.5
Stomach—complete emptying	4.6	5.5
Large intestine—first appearance	3.3	4.2
Large intestine—duration of meals	22.5	31.7
Complete clearance from large intestine	25.5	38.6

Plate XXII



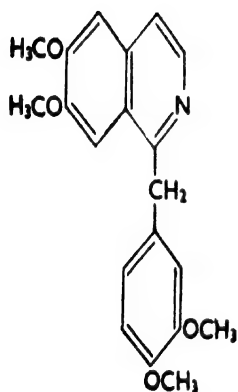
Morphine

FIG. 59(a)



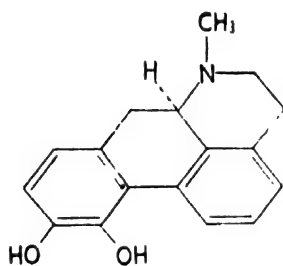
Codeine

FIG. 59(b)



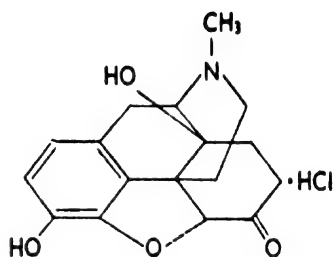
Papaverine

FIG. 59(c)



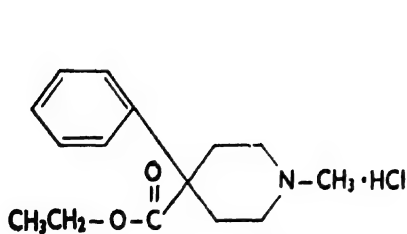
Apoinorphine

FIG. 59(d)



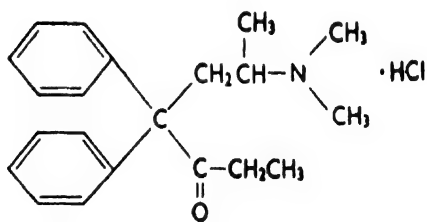
Oxymorphone hydrochloride

FIG. 59(e)



Meperidine hydrochloride

FIG. 59(f)



Methadone hydrochloride

FIG. 59(g)

FIG. 59 Structural formulae of important morphine derivatives and substitutes

Plate XXIII

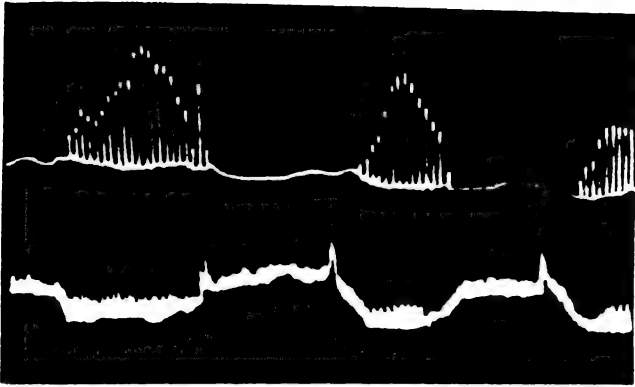


FIG. 60 *Depressant effect of morphine on respiration:* at (1) morphine has been administered. Note Cheyne Stoke respiration,

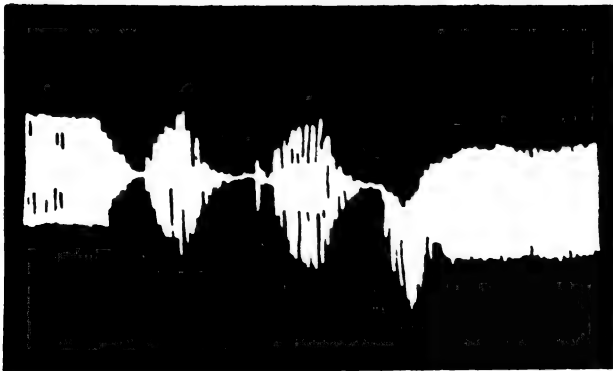


FIG. 61 *Morphine nalorphine antagonism on respiration:* Morphine given at (1) caused respiratory depression which was restored to normal by nalorphine (X).

(c) Morphia is a capital drug for the relief of colic pain, which if uncombined with atropine, is of central origin.

(d) Morphine emesis, though mostly central, is partly antagonised by atropine.

(e) Opium and morphia thus are sedatives and anodynes for intestine and capital drugs for colic pains and diarrhoeas.

Other effects : (a) Morphine causes increased intrabiliary pressure and spasms which are relieved by nitrites and not by atropine. Relief of biliary colic by morphia is of central origin, though because of its peripheral effect, it is usually contraindicated.

(b) There is spasm of the sphinder vesicae with increased tone of the detrusor muscle.

(c) In threatened abortion there is a sedative action for which it is sometimes used.

(d) There is also a mild p-sympathomimetic effect from the inactivation of cholinesterase, a mild vagal effect on the heart which is antagonised by atropine. In toxic doses there is a fall of B.P. and tachycardia, coronary vessels may be dilated. Finally death occurs from the respiratory but not primarily from cardiac failure.

(e) There is a transient hyperglycaemia and disturbances in protein, fat and water metabolism mostly in chronic addicts.

(f) The L.D. dose of morphia usually is 100-200 mg but morphinomans can stand sometimes as high as 5 gm. i.e. 25-50 lethal doses with impunity.

Actions Compared : (a) Compared to opium which contains all the active principles, morphine action is quicker, precise and with less G.I. upset and less diaphoresis.

(b) Compared to atropine, there is C.N.S. depression and not stimulation, myosis and not mydriosis, spasmogenic and not antispasmodic action and finally diaphoretic and not anhydrotic effect as with atropine.

Toxicology: These are (a) acute and (b) chronic and both alarming, devastating and difficultly manageable. *Chronic toxicity* is dealt with in the section of the problem of addiction at the end of the chapter.

Acute toxic effects : have the following characteristics:

(a) Euphoria from the depression of the higher inhibitory centres.

(b) All the feelings are blunted—pain, fatigue, malaise and gloominess.

(c) The body appears to be heavy like lead.

(d) A dreamy state of mind and finally.

(e) Somnolence — coma — respiratory failure and death.

Management : (a) gastric lavage with KMnO_4 lotion (60 mg/30 ml) to oxidise the alkaloid. (b) Traditional analeptics: coramine—2.5 ml. IM, $\text{CO}_2 + \text{O}_2$ mixture and also atropine. (c) Finally the new specific drug—nalorphine, the morphine analogue, acting by competitive blockade and detailed at the end of the chapter. The outcome is fairly satisfactory if early diagnosis has been made.

Uses: Based on the actions described—(a) analgesic (b) hypnotic, (c) cough sedative—a drug ranking high in relieving pain and giving rest to the patient. The *aphorisms of Sydenham* that 'Few doctors would have courage to practise medicine without opium and of Osler—'God's own medicine', have been true even upto the recent times, when its place has been taken up by newer substitutes and other drugs.

Topical : (a) Anodyne use of Landanum has been discarded now. (b) Dionine drop in glaucoma is still used.

Systemic : 1. *Relief of visceral pain:* (a) cardiac, (b) pulmonary, (c) intestinal, (d) neoplastic, (e) acute pericardial and peritoneal. It is an invaluable drug in cardiac dyspnoea pulmonary oedema, coronary thrombosis and shock conditions giving rest to the patient, relieving pain and permitting collateral circulation to be established.

2. *Respiratory and G.I. disorders :* (a) irritable cough, (b) pain of pleurisy, pneumothorax and acute abdominal troubles.

3. As a *hypnotic* only if the insomnia is due to pain but pethidine is preferred. Further compared to barbiturates, it is however a poor sedative and anticonvulsant.

4. *Haemorrhages*—haemoptysis or haematemesis. but to beware of the cirrhosis of liver.

5. *Prenaesthetic medication* and obstetrical analgesia; but in view of provoking respiratory depression in the new born, hyoscine HBr and barbiturates are preferred.

Limiting Factors : (a) Respiratory depression, (b) paralytic ileus, (c) tachyphylaxis, (d) drug habit.

Contraindications : (a) infancy and old age, (b) cirrhosis of liver, (c) myxoedema, (d) head injury, surgical shock and acute abdomen, before the diagnosis is made, (e) after cholecystectomy, due to biliary spasm.

OTHER ALKALOIDS, DERIVATIVES AND SUBSTITUTES

The limiting factors of morphia have brought under the field of research, other alkaloids of opium, derivatives and substitutes, which are as follows:

Morphine ethers	Codeine Thebaine Dionine.	Methyl morphine dimethyl morphine ethyl morphine	natural do derivative
Morphine esters	Heroin	discetyl morphine	derivative
Oxidation products	Dilrudid Eucodal	dihydroxy derivatives	
Other products	Pantopan Apomorphine		
Morphine substitutes		Pethidine Methedone Levorphanol Levo-dromoran	Synthetic

Chemistry: The structural formulae of some of these important compounds is given in Plate XXII. Figs. 59—(a)-(f). An analysis of these structures reveals the following:

Morphine	HO C ₁₇ H ₁₇ ONOH	
Codeine	CH ₃ O C ₁₇ H ₁₇ ON OH	1 methoxy group
Thebaine	CH ₃ OC ₁₇ H ₁₇ ON OCH ₃	2 methoxy group
Dionine	C ₂ H ₃ O C ₁₇ H ₁₇ ON OH	1 ethoxy group
Heroin	CH ₃ COO C ₁₇ H ₁₇ ON OCOCH ₃	Acetylation of both the OH groups.

- The analgesic effect is linked to the two OH groups in morphia.
- Codeine is much less depressant because of the methoxy group.
- Thebaine is even strongly convulsant.
- Heroin is more depressant and more addictive.

Codeine: The phosphate salt is crystalline and bitter. *Dose* 15-60 mg; *Linctus* and *Syrup-codeine phos*: 2-4 ml.

Action: Compared to morphine, it has 1/20 narcotic effect but 1/3 action on the cough centre. It is thus inferior in analgesic action but superior to morphine for relieving cough. It causes less nausea, vomiting, constipation, respiratory depression and addiction. It is still much used for irritating cough and visceral pain, particularly in children, in whom, because of the sensitive respiratory centre, morphia is contra-indicated.

Papaverine: A natural alkaloid of the insoquinoline group with little narcotic or analgesic action. It is a potent antispasmodic for smooth

muscles, particularly of blood vessels—coronary, cerebral, pulmonary and peripheral arteries. It increases the refractory period of the cardiac muscle and reduces the tendency for fibrillation.

The sulphate or the HCl salt is used in *doses* of 0.12 to 0.5 gm./os/parenterally. It is sometimes used in coronary occlusion, vascular encephalopathy and pulmonary embolism.

Dionine: Its actions are intermediate between morphine and codeine. It relieves dry hacking cough without depressing the respiration, in *doses* of 15 mg. It is useful in bronchitis, whooping cough and also in glaucoma, iritis and corneal ulcer as 6% solution or ointment.

Heroine: Diacetyl morphine is 4-8 times more potent and more toxic than morphine and produces worst addiction, maximum euphoria and worst criminal tendency. It is liked by addicts but should never be used excepting in the terminal stages of cancer. *Dose*—2.5 to 7.5 mg.

Dilaudid: It is more potent, less constipating and probably causes less tolerance formation. *Dose:* 4 mg/os.

Eukodal: 5-20 mg. and has similar action. *Metopan:* 5 mg./os. It is twice as analgesic as morphine, is devoid of emetic action and is less depressant to the respiration. *Pantopan:* 10-20 mg. tab. or pill. It contains all the alkaloids of opium with 50% morphine. It is an antispasmodic of value for G.I. irritation and cough. *Apomorphine:* an anhydride product of morphine and a central emetic producing retching even after the stomach is removed. It has little narcotic action. *Dose:* 5-10 mg.

Pethidine or Meperidine: The hydrochloride salt is colourless, crystalline powder with a bitter taste. It is soluble in water. *Dose*—100 mg.

Action: (a) It combines the analgesic effect of morphine and the antispasmodic effect of atropine. Its effect on the pupil, heart and bronchus resembles atropine, but on the gut and blood vessels, that of papaverine. There is rise in intrabiliary pressure like morphia but no constipation. (b) It is a much less respiratory, depressant and habit forming than morphine, but not free from tolerance, addiction or withdrawal symptoms. (c) It is rapidly destroyed in the liver, is very little excreted in the urine, and is more effective parenterally.

Uses: Same as morphine: coronary infarction and other visceral pains, obstetric analgesia and as antispasmodic. It has taken away the place of morphine in the majority of cases, in therapeutics.

Methadone HCl: 2.5-10 mg./os or S.C. It is less narcotic than mor-

phine, but stronger analgesic than pethidine. It is used as a substitute for the former, during its withdrawal.

	<i>Morphine</i>	<i>Pethidine</i>	<i>Methadone</i>
Sources	Natural alkaloid	Synthetic	Synthetic
Sedation and analgesia	+++	++	++
Euphoria	++	±	+
Smooth muscle	Spasmogenic	Antispasmodic	Inconstant effect
Addiction	++	±	+

Phenadoxone: 10-30 mg./S.C. It causes appreciable analgesia, but less hypnosis and addiction, *Domoran*: (levorphanol) It is thrice as active as morphia with longer duration of action. It is sometimes used for the relief of intractable pain of malignancy, in a dose of 2 mg.

NEWER DERIVATIVES AND SUBSTITUTES

Oxymorphone (Numrophan): It is 14-hydroxydihydro morphinone and is 8 times more potent as an analgesic and evokes less nausea and vomiting.

Normorphine: a N-demethylated derivative of morphine, which is less potent and less toxic than morphine.

Anileridine: It is available as HCl salt for the oral and the phosphate salt for parenteral administration. It is more potent than pethidine but less so than morphine, as an analgesic. It also exhibits antitussive action. *Dose:* 15-30 mg/oral/S.C.

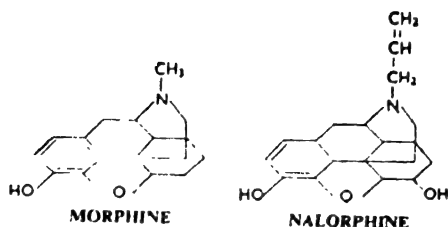
Nisentil HCl: A useful adjunct for obstetrical analgesia and is as potent as pethidine with a similar margin of safety. *Dose* 40 mg. S.C.

Alvodine: An addictive analgesic, more potent than morphine and is used as ethanosulphonate salt. *Dose:* 10-20 mg. S.C. or I.M.; orally—25-50 mg.

It is evident that in spite of all these studies, an ideal analgesic free from addiction liabilities and tolerance, has yet to be discovered. Morphine and particularly its substitutes, however have still to be used in a large number of conditions, in which relief of visceral pain is imperative. Morphine is also used by a number of people as a *dope* for which an effective, antidote, nalorphine, a morphia analogue, has recently been discovered, which finds its use in all acute poisoning cases with respiratory depression and other serious symptoms, as detailed hereafter. It is of little or no therapeutic value in the treatment of chronic morphia addictions.

NALORPHINE

This is a new drug which has been introduced by the Unna group of workers in recent years. Chemically, it is N-allyl morphine. It differs from morphine in having an allyl group at the N position, as shown below:

*Illus. XIV Structural difference between morphine and nalorphine*

The drug is available in the form of Inj. Nalorphine hydrochloride 0.5%, one and two ml. amps. It is poorly absorbed orally, conjugated in the liver and excreted in the urine.

Actions: (a) It specifically antagonises the respiratory depression of morphine almost instantaneously (Plate XXIII; Fig. 61).

(b) It also antagonises the hypotension, coma, antidiuresis and smooth muscle spasms provoked by the high doses by morphine.

(c) It itself produces mild analgesis, hypnosis, respiratory depression, relaxation of smooth muscles and mild entitussive action.

(d) It does not produce any addiction but it causes withdrawal symptoms in morphine addicts.

(e) Besides morphia, it also antagonises pethidine, methadone and levorphanol, but not barbiturates.

Mode of Action : Not definitely settled. The following have been suggested:

(a) End-organ competition, (b) Therapeutic interference, (c) Enzymatic type of substrate competition.

Uses: (a) Morphine poisoning: 10 mg. I.V. every 15 mins, not exceeding a total dose of 40 mg. The respiration becomes normal in 3-4 mins and so also the cyanosis.

(b) Neonatal respiratory depression; secondary to sedation. It is

sometimes given to the mother also as a preventing measure, before the delivery.

(c) Diagnosis of morphine addiction: 5-8 mg. of nalorphine produces immediate withdrawal symptoms.

(d) It is also sometimes used with morphia to obtain analgesia without risk of respiratory depression and addiction.

PROBLEM OF DRUG ADDICTION

This is a knotty problem which is not only on the increase, practically in every country but is also affecting the lower age group of the population. In reality, it is a multifaceted social problem which has deep roots in the social set up of the modern era, as well as, in the mental make up of the addicts. Further, with the advances in drug industry and the discovery of a large number of potent synthetic drugs, including psychopharmacological agents and mood elevators, with addiction liabilities, coupled with their ease of availability, the incidence of addiction is further on the increase. Whatever may be the background, there is no denying the fact that drug addiction is a very serious problem which, if unchecked, leads to moral depravity and far-reaching rehabilitation difficulties.

Drug addiction is, in reality, a psycho-somatic condition being about 80 to 90 percent psychopathic and the rest somatic. It comprises the following three aspects each affecting the normal functioning of the body:

1. Habituation: which is mostly of psychic nature.
2. Tolerance: which is mostly biochemical.
3. Dependence: which is an altered physiological state induced by the drug.

Habituation: This starts from an emotional dependence for euphoria, relief of anxiety and tension, by repeated use of the drug, to which the system becomes accustomed and cannot do without it.

Tolerance: It is an unusual resistance to ordinary doses of a drug and may be (a) natural and congenital or (b) acquired by repeated uses.

It may depend on the following factors: (a) poor absorption, (b) rapid excretion, (c) rapid detoxification, (d) cellular acclimatisation or adaptation, most of which involve enzymetic processes.

Tachyphylaxis: It is an acute tolerance due to absorption or union of the drug with the receptor substance in the target cells which thwarts subsequent responses. This is often found with ephedrine.

Dependence: This is a condition in which the addict cannot do without the drug. This is not only because of the action of the drug on the C.N.S. but also because of the gross biochemical changes that have been produced by the drug including opening of newer enzymatic pathways of metabolism requiring the drug and its metabolites for its functioning. There is thus distortion of homoeostasis which is partially compensated by functional adjustments but disturbed again by increased doses, leading to over compensation and this vicious cycle continues. When the drug is withdrawn, the system finds itself in a state of biochemical and physiological imbalance, producing devastating withdrawal symptoms.

According to Tatum and Seever's dual hypothesis, morphine produces a biphasic response of both excitation and depression according to its action with different parts of the C.N.S. as well as on the receptors at the cell surface or intracellularly. One of these actions is responsible for provoking sensitivity, while the other, the resistance formation, as observed with morphine. Further, according to Axelrod, the receptors of morphine and its dimethylating enzymes, are similar. When the enzyme is inactivated, the receptors remain engaged and thus tolerance is produced.

Signs and Symptoms: (a) Moral depravity—the morphine addicts are habitual liars.

(b) Anaemia, indolence, muscle wasting, tremors and skin troubles.

(c) Anorexia, constipation, insomnia, impotence.

(d) Changes in blood chemistry and high cholesterol level in the addicts.

The diagnosis of drug addiction is not always very easy as the addicts often continue their normal activities without physical and mental signs. (a) pinpoint pupil, (b) evidence of pricks, (c) injection of morphine not producing C.N.S. depression and (d) withdrawal symptoms are some of the diagnostic signs.

Withdrawal Symptoms: They differ according to the degree of addiction and may be *mild, moderate, marked* and *severe*.

(a) Mild: Yawing, lacrimation, rhinorrhoea and perspiration.

(b) Moderate: Tremors, goose flesh, anorexia and mydriasis.

(c) Marked: Rise in temperature and B.P., restlessness and insomnia.

(d) Severe: Vomiting, diarrhoea, loss of weight, V.M. paresis and collapse.

These symptoms start within 8 hours of abstinence, become maximum at 40 hours and subside in 10 days. An addict stabilised on 60 mg.

Q.D.S. of morphine, develops these symptoms immediately after 15 mg. of nalorphine S.C.

Treatment : (a) Difficult and painstaking, requiring special set up, hospitalisation and also rehabilitation facilities.

(b) Sudden and gradual withdrawal of morphine, substituted by non-habit forming hypnotics or analgesics e.g. scopolamine, bromides, amytal and methadone.

(c) Psycho-occupational therapies, proper type of follow up, and also change of environment.

(d) Lastly, concomitant use of *nalorphine*, specific antidote, for obtaining analgesic effect without addiction.

In spite of all these, the prospect for complete success without reverting to the habit is not very bright, unless the addict himself develops a strong reaction and will-power to give up this deplorable habit.

THERAPEUTIC APPLICATIONS

Both these groups of drugs—*alcohol* and *opium* alkaloids—have extensive pharmacological actions but in actual practice, limited therapeutic applications.

1. The use of alcohol today is limited to its topical application for the cleansing, sterilisation and hardening of the skin, as well as, its local application for toothache, sciatica and trigeminal neuralgia.

2. Morphine and its substitutes are still used in a number of conditions such as (a) coronary infarction, (b) renal and other colics, (c) burns and other shock conditions, (d) pre-anaesthetic medication and obstetrical analgesia. As a general rule, *pethidine* is preferred to morphia, in all these conditions, because of its lesser addiction liabilities. Morphia however is still sometimes used where the response to pethidine is not fully satisfactory. *Codeine* is used as a cough sedative and *dionine* for relief of pain in acute glaucoma. *Horioine* and *leverophenol* are sometimes used for the relief of intractable pains of malignancy when all other drugs fail. *Methadone* is often used as a substitute for morphia during the withdrawal of the latter in chronic addicts. So far as *nalorphine* is concerned, as a physiological antidote, with dramatic action, it finds its use in acute morphia and several other conditions indicated in the text.

CHAPTER

26

PHARMACOLOGIC RESPONSES OF THE RESPIRATORY SYSTEM

PHYSIOLOGICAL CONSIDERATIONS. RESPIRATORY GASES—THEIR ROLE AND USES. BRONCHIAL ANTISPASMODICS, ANTITUSSIVE AND EXPEC- TORANT DRUGS. MODE OF ACTION AND THERAPEUTIC USES

[The respiratory system, comprising *respiratory* and *cough centres*, as well as respiratory tract, is sensitive to the action of a number of gases and chemical agents. The *inspiratory*, *expiratory* and *pneumotoxic*, *coughing* and *vomiting centres*, are closely situated and reflexly regulated by vagal, carotid sinus and olfactory impulses, which are also influenced by drugs. The inspiratory centre is highly sensitive to pH changes and also CO_2 and O_2 tensions. Oxygen therapy, by any of the standard techniques — catheter, mask or tent, is an important corollary in the therapy of many diseases, accompanied with hypoxia from pulmonary, cardiac, space-flight, mountaineering and diving episodes. Similarly, CO_2 , which is an important stimulant of the respiratory centre, is of therapeutic use in respiratory depression, asphyxia, coma and carbon mono-oxide poisoning. It is also used with general anaesthetics for increased ventilation and speed of induction. Helium, in compressed form, like O_2 and CO_2 , is sometimes used in respiratory obstruction and in decompression sicknesses.

Other drugs, acting on the respiratory system, are: (a) Bronchial antispasmodics (b) Antitussive and (c) Expectorants.

The *Antispasmodics* comprising principally sympathomimetics, parasympatholytic and directly acting drugs, along with corticosteroids and anti-histaminics, find their uses, principally in *bronchial asthma*. The *antitussive cough suppressants*—the time honoured opiates and also a number of newer compounds of non-addictive nature — mescaline, dimethoxanate and benzonatate, besides, antihistaminics, are used for sedating the cough centre, as well as, cough reflexes. The *stimulant expectorants* comprising tar and essential oil, salines, ipecac, senega and glycyrrhiza, which act mostly by facilitating the expectoration, are seldom used now in upper respiratory tract infections, chronic bronchitis and bronchiectasis, their places being mostly taken away by specific chemotherapeutic, antibiotic and proprietary pharmaceutical combinations.]

The chapter should normally comprise drugs acting on the respiratory and cough centres, as well as, on the respiratory tract, alleviating cough reflexes and facilitating expectoration. The analeptics or res-

piratory stimulants having already been discussed earlier, it is proposed to undertake the study of the following in this chapter.

- (a) Oxygen, carbondioxide and helium therapy.
- (b) Antitussives and expectorant drugs.
- (c) Bronchial antispasmodics.

Physiological Considerations: The function of respiration is to supply oxygen to the various tissues of the body, remove excess of carbon-dioxide formed during the process of cellular metabolism and regulate body temperature through heat loss. In addition, it also serves as a channel of excretion for the volatile products of metabolism. The inspired air is carried to the alveoli through the bronchial tree, lined by ciliated epithelium, which prevents the entry of any foreign particles into the alveoli. It is supplied by the motor vagus and the inhibitory sympathetic nerves. The gaseous exchange takes place through the spacious alveolar surface of about 70 sq. meters, the rate of exchange depending on the vascularity of alveoli and the differential tension of gases in the blood and air.

The velocity of air/sec., in different parts in the pulmonary tract, is about 4 meters in the glottis, 1 meter in the large and 0.1 meter in the small bronchi, during quiet breathing. During forced breathing, this velocity may increase tenfold and during the act of coughing, 60 miles/hr. or 1 mile/m_t., which is the velocity of wind in a gale.

Efficiency of respiration is determined by the rate and rhythm of respiration and the 'patency' of the respiratory passages and this is adjusted according to varying needs of the body, inasmuch as, the tidal air which is about 300 ml. at rest, may increase 15-fold, after heavy exercise.

Centres : The *respiratory centre*, which comprises inspiratory, expiratory and pneumotaxic centres, is situated in the floor of the 4th ventricle. The accessory centres for coughing and vomiting are also close to it.

The centre is reflexly regulated by the afferent vagal impulses from the stretch receptors in the lungs, the chemo and pressor receptors in the carotid body and the sinus and the afferent impulses from the olfactory and other cutaneous nerves. The inspiratory centre is highly sensitive to changes in tension of CO₂ and O₂ and pH.

Cough is a protective reflex for expulsion of sputum from the respiratory tract and alveoli. It comprises a deep inspiration, followed by a forced expiration, against a closed glottis, which then

suddenly opens when the intrathoracic pressure is high. It corresponds to the act of vomiting in this respect.

The cough reflex originates from the respiratory mucosa, pleura, diaphragm or abdominal and thoracic organs. The tussal impulse is carried to the cough centre in the medulla, close to the vomiting and vagal centres. The efferent path is to the diaphragm, intercostal and the accessory respiratory muscles, which participate in the action of coughing.

Methods of Evaluation: These may refer to the study of respiratory stimulants, as well as bronchial antispasmodic, antitussive and expectorant drugs. (a) The study of analeptics is carried out in drug-induced depressed conditions of the centre, with *anaesthetics*, *morphine* or *barbiturates* and thereafter, studying the stimulant effect of the test drugs, (b) The bronchial antispasmodics are studied in *histamine* or *pilocarpine* induced bronchoconstriction or isolated tracheal preparation in guinea pigs, (c) the antitussive and expectorants are evaluated by producing irritation and artificial cough with the vapour of irritant substances like *formaldehyde*, *carbolic acid* etc. These methods are fairly qualitative and meant for the preliminary screening of drugs only as the underlying changes, do not simulate the clinical conditions, (d) Steriotaxic techniques also used for the evaluation of antitussive drugs.

OXYGEN, CARBON DIOXIDE AND HELIUM THERAPY

These gases, besides their important physiological roles, also find their uses in a number of conditions. They are included in this chapter because of their mode of administration and also respiratory action.

OXYGEN

General Considerations: Oxygen helps in the various oxidative processes, taking place in the tissues and for which purpose, it is carried from the lungs to the tissues by blood, partly dissolved and partly loosely combined with haemoglobin. The oxygen carriage, besides other factors, also depends upon the pressure at which oxygen is present in the inhaled air.

Of the three vital necessities of life — *food*, *water* and *oxygen*, deficiency of the last is most rapidly fatal. Still our knowledge about the physiological role of oxygen was to come as late as in 1772, as a result of the work of Priestley and Lavoisier. The first therapeutic use of

oxygen was made in 1794 with such overenthusiasm and indiscrimination that the initial failures quickly damped the tiding spirits of the investigators and it was left to later scientists, like *Haldane*, *Hill*, *Barcroft* and *Krogh* to put *oxygenotherapy* on a sound footing.

Hypoxia : Whenever there is increased demand for oxygen as during physical exercises or from the reduced quantity of oxygen in the air, its resulting deficiency in the blood, stimulates the chemoreceptors and the respiratory centres and the increased rate of respiration tries to normalise the condition. The normal reserve capacity of the lungs to expand is considerable and therefore, the person has no difficulty in adjusting himself. However, if this reserve capacity is less, as in pulmonary diseases like pneumonia, emphysema etc., there is, difficulty in breathing, associated with hypoxia.

It is evident that through *dyspnoea* it can be taken as an indication of *hypoxia*, treatment cannot be delayed till this develops, because hypoxia occurs long before dyspnoea and has to be recognised in time.

Similarly, during hypoxia, a large quantity of haemoglobin is present in a reduced state and when this exceeds 5 gm/100 ml, *cyanosis* occurs. This is dependent to a large extent, on the total haemoglobin content of the blood. Hence, an anaemic patient may not exhibit cyanosis though he may be severely hypoxic.

Causes : (a) Low atmospheric oxygen content (high altitudes), (b) Poor diffusion in lung (lung diseases), (c) Poor carrying capacity of blood (anaemia and carbonmonoxide poisoning), (d) Poor blood supply to a part (thrombosis of vessels), (e) Non-utilisation of oxygen in tissue, due to poisoning of enzymes with cyanides.

Effects : Besides the lowering of the blood oxygen concentration and cyanosis, there is an increase in the rate of respiration and heart and also rise of blood pressure. Prolonged hypoxia causes paralysis of the vital centres and death. So, hypoxia not only stops the machine but wrecks the machinery, as Haldane had so succinctly put.

Effects of excess oxygen in air : The blood O_2 increases so much that even the dissolved oxygen becomes enough to meet with the tissue requirements, with the result, that oxyhaemoglobin does not dissociate into haemoglobin and oxygen. For the carriage of CO_2 from the tissues to the blood, the presence of free haemoglobin is necessary. Its lack leads to the increase in CO_2 pressure inside the tissues. High O_2 concentration also lowers the nitrogen-content of blood.

Immediate effect of inhalation of 100% O_2 , leads in a transient respiratory depression, because of the lack of stimulation of chemoreceptors and through them, the respiratory centres. Later on, the respiration is stimulated, heart rate decreases, cardiac output is

lowered but B.P. hardly changes. If in any patient, after giving oxygen; the pulse rate drops by more than 10 counts in a minute, it may be taken that hypoxia has occurred.

Respiratory toxicity : The effects of breathing high concentration of oxygen for a long time can be bad and can cause tracheobronchitis and alveolar oedema, due to irritation.

C.N.S. toxicity : When O_2 is breathed in a concentration greater than 2 atm. pressure, C.N.S. symptoms like muscular twitchings, nausea vertigo, loss of sensations, convulsions and unconsciousness may occur.

Other bad effects: (i) Retrolental fibroplasia, causing blindness in premature infants, (ii) Respiratory depression, and (iii) Pulmonary collapse, due to oedema.

However, it has to be remembered that by the methods, with which oxygen is usually administered, its level can never exceed 50%, in which concentration, it is not toxic. Further, the untoward effects of hypoxia are worse than those of excess of oxygen.

Mode of Administration: Oxygen is available, in compressed form in cylinders, fitted with a valve. Cylinders are colour-coded and can be refilled after use. Its mode of administration comprises the following devices:

1. **Nasal catheter :** Oxygen is bubbled through water for humidification and is then passed through a soft catheter into the nasopharynx. It is a convenient method but the concentration of oxygen given by this method, is very low—0.2 litres as against the requirement of 3-4 liters/minute.

2. **Face mask :** It is more expensive but efficient, meeting with less than 50% of the requirement of the patient.

3. **Oxygen tents or hood :** For this, a large quantity of oxygen is required. It is suited for infants, particularly. Other routes like rectal and intravenous, have almost been discarded.

Uses: Oxygen therapy is used with the following two specific purposes in view: (a) For combatting hypoxia occurring from any of the underlying causes. (b) For displacing other gases like nitrogen from the body in high concentrations.

1. Oxygen therapy finds its primary indications for use for relieving any *hypoxic state*, which may be resulting from:

(a) Inadequate oxygenation of healthy lungs as in high and low altitudes: space flights, mountaineering, deep sea diving.

- (b) Lung diseases: pneumonia, pulmonary oedema, emphysema and fibrosis.
- (c) Cardiac conditions : acute left ventricular failure, coronary thrombosis, cor pulmonale.
- (d) Severe anaemia.

2. Oxygen therapy is also frequently used for displacing other gases and counteracting their toxicities, as in:

- (a) Caisson's disease for reducing the nitrogen content of blood.
- (b) Carbonmonoxide poisoning.
- (c) As a diluant of anaesthetic gases.
- (d) In anaerobic infections for killing the organisms.
- (e) After pneumoencephalography.
- (f) Spontaneous pneumothorax.
- (g) Paralytic ileus with abdominal distension.
- (h) Acute respiratory distress in pulmonary embolism.
- (i) In avascular malignant tissues, the susceptibility to radiations is increased by oxygen.

For conditions in (b) & (d) (c) & (i) 'hyperbaric oxygen', i.e. under 2-3 atmospheric pressure, is administered.

CARBONDIOXIDE

General Considerations: Since the discovery of *Lavoisier* and *Miesher* on the role of CO_2 on the respiration, it is now established that the gas plays an important role in the regulation of vital functions in the body and small changes in its concentration produce marked effects on the respiration, circulation and C.N.S. functions.

CO_2 produced during the various metabolic processes, is diffused from the cells into the blood stream, where, it is carried as bicarbonate ion, in combination with haemoglobin and plasma proteins, and also in solution. This is carried in the mixed venous blood to the lungs from where it is exhaled out.

Actions: These involve (a) Respiration, (b) Circulation and (c) CNS.

Respiration: It is a potent stimulant of the respiration. Inhalation of 2% CO_2 increases the rate and depth of respiration immediately. The effect increases to its maximum up to 10% concentration. The action appears to be produced directly on the respiratory centre, as well as, reflexly, through the arterial chemoreceptors.

Circulation : Here again the action is both direct, as well as, centrally mediated, through the ANS. The direct effect on the heart, results in its diminished contractile force, slowing of the rate and vasodilatation, the rhythm is normally not affected. The autonomic action results from a widespread activation of the sympathetic nervous systems with increased epinephrine/nor-epinephrine plasma level. The response is mediated through the sub-cortical hypothalamic centres, brain stem, reticular formation and medulla. The sympathetic effect, comprises an increased force and rate of cardiac contractions and constriction of the vascular beds. The overall effect in a normal man is, increased cardiac output and heart rate, elevation of systolic and diastolic pressure and increase in pulse pressure. When 6.5% CO_2 is inhaled, there may be an increase in the cardiac output by 50%, mean arterial pressure, by 30% and heart rate, by 20%, indicating thereby, a decrease in the total peripheral resistance. CO_2 does not induce cardiac arrhythmia but may exaggerate that produced by cyclopropane. The important circulatory beds affected by CO_2 , are the cerebral and coronary circulations. The pulmonary vasculature is very little affected. All these effects disappear quickly after withdrawal of CO_2 .

Central Nervous System : Inhalation of low concentrations of CO_2 , depresses cortical excitability and increases the threshold for drug induced or electroshock seizures. With high concentrations, the subcortical areas are activated, which overcome the depressant action on the cortex. The increased cortical excitability may even lead to convulsions. It also produces E.E.G. changes.

Untoward Effects : At 5-6% concentration, there is increased respiration and acid taste, but rarely any dyspnoea, which is produced at 10% concentration, along with, headache, dizziness, sweating, restlessness and paraesthesia. An abrupt withdrawal also produces headache and dizziness. There may be elevation of blood pressure, tachycardia arrhythmias, following inhalations of CO_2 .

Mode of Administration: (a) In metal cylinders compressed to 58 atmospheres, for inhalation purposes. The rebreathing technique is also used in certain cases. (b) Sticks and snows for local cauterising effect are also in use.

Uses: (a) Respiratory depression, asphyxia or coma,
 (b) Carbon monoxide poisoning.
 (c) Along with general anaesthetics, for increasing the speed of induction and recovery from anaesthesia, by improving respiration.

- (d) As a diagnostic agent for measuring the depth of respiratory depression.
- (e) Persistent hiccoughs — 10-15% concentration is used.
- (f) Potitmal epilepsy for terminating the seizures.
- (g) Local use for warts and naevus.
- (h) Aerated drinks act as carminatives in acute indigestion.

HELIUM

An inert gas, having low density and solubility. Its low density permits the breathing of helium oxygen mixture without efforts in cases of respiratory obstruction. While its low solubility prevents the risk of gas embolisms and nitrogen narcosis, in divers working at high pressure, breathing compressed air.

Mode of Administration : (a) In compressed form, containing 95% of helium and 5% of nitrogen in steel cylinders.

(b) In combination with oxygen, through face mask or by non-rebreathing techniques.

Uses: (a) Respiratory obstruction. (b) Decompression sickness or Caisson's disease. (c) As a diluent with cyclopropane and oxygen, for decreasing inflammability.

BRONCHIAL ANTISPASMODICS

These are a group of heterogenous drugs which relieve bronchial spasms by diverse mechanisms. The important ones are:

1. *Sympathomimetics* — Adrenaline, Ephedrine and Isoprenaline.
2. *Parasympatholytics* — Atropine, Derivatives and Substitutes.
3. *Xanthines* — Theophylline and Aminophylline.
4. *Benzyl isoquinoline* — Papaverine.

The first two groups act through the autonomic receptors while the last two, directly on the plain muscles of bronchioles and other organs.

The bronchial antispasmodics constitute an important group of therapeutic agents and are often life saving giving relief to conditions characterised by *acute spasms* as in *bronchial asthma*. Some of them also exhibit antisecretary and expectorant action and find uses in whooping cough.

In addition to above, *antihistaminics* and A.C.T.H. are also of great value in bronchial spasms and are frequently used in acute asthma,

while the nitrites which also exercise plain muscle relaxant effects, are used more for blood vessel spasms in anginal and other conditions.

All these drugs have been studied in their respective chapters, as well as, in the chapter of antispasmodic, in which, their spectrum of therapeutic uses, also fully elaborated.

ANTITUSSIVE DRUGS

Relief or cure of cough in pulmonary infections can be achieved by some of the following measures:

(a) Symptomatic relief by cough suppressants, (b) Symptomatic relief by cough stimulants and expectorants, (c) Use of antibiotics, chemotherapeutic and other agents, dealing with the causative organism.

The last group being included in the chapter of chemotherapy, only the remaining two will be discussed here.

COUGH SUPPRESSANTS

These drugs depress cough reflexes mainly by inhibiting the passage of the tussal impulses through the coordinating areas in the medulla. They comprise old and new synthetic drugs of promise, whose real efficacy has yet to be substantiated by wider and more controlled clinical appraisals.

Narcotic or addictive antitussives.	Opiates, codeine and methadone.
Nonaddictive antitussives.	Dextromethorphan, noscapine, 1-propoxyphene.
Antihistaminics.	Dimethoxanate.
Local anaesthetics.	Benzonatate, carbetapentane.

Opiates: Though they comprise most of the alkaloids and derivatives of opium and morphine, they are hardly used in current therapeutics, due to the limitation of central respiratory depression, produced by them. However, *syrup codeine phos.* which is not only effective but is also quite often used by clinicians, as cough sedative. The opiates are still sometimes used in severe, exhausting and intractable cough, for short term therapy.

Dextromethorphen HBr (Romilar): A non-analgesic, non-addictive antitussive agent, available as *tablets* of 15 mg. and *syrup* 3 mg/ml.

Its antitussive activity is equal to that of codeine. *Dose:* 10-20 mg. q.d.s.

Noscapine (Narcotine): A benzyl isoquinoline alkaloid of opium which combines antitussive and smooth muscle relaxant properties. *Dose:* 15-30 mg. t.d.s.

1-Propoxyphene (Novrad): A levo-isomer of darvon nonaddictive analgesic but devoid of analgesic action. It is 1/3rd as active as codeine as cough depressant without producing any constipation or tolerance. *Dose:* 50-100 mg. t.d.s.

Dimethoxanate HCl (Cothra): A phenothiazine derivative, which is available as syrup, containing 5 mg/ml. *Dose:* 25-50 mg. t.d.s. Its action starts in 10 minutes and lasts for 4 hours. It effectively palliates acute coughs, better than severe chronic ones.

Benzonatate (Tessalon): Its antitussive action is not entirely central, but is also mediated through its anaesthetic effect on the sensory receptors of the vagal efferent fibres involved in cough. It is available in capsules of 50 and 100 mg. *Dose:* 100 mg. 3-4 times a day. Its action starts in 10-20 minutes and lasts for 2-3 hrs.

Carbetapentane Citrate: An antitussive agent with local anaesthetic and atropine like properties. It is available as tablets and syrup. *Dose:* 15-20 mg. t.d.s.

COUGH STIMULANTS AND EXPECTORANTS

This group of drugs stimulates cough reflexes directly by diverse mechanisms: (a) fluidification of tenacious sputum, (b) induction of productive cough and (c) clearing of the passage, all of which together, bring relief to the patient.

The *expectorants* also produce similar actions, but they are more directly concerned with the removal of sputum from the respiratory passages. The removal of tenacious sputum results in a demulcent and protective action on the inflamed surfaces and as productive cough sets in, the patient feels less exhausted and more restful than before.

CLASSIFICATION

Stimulant expectorants	Tar derivatives, camphor, gum benzoin, balsam of tolu, eucalyptus.
Salines or fluidifying agents	Iodides, ammonium salts, citrates and acetates.
Nauseant or reflex expectorants	Ipecac, senega, scilla, tartar emetic.
Demulcents or sedative expectorants	Glycyrrhiza, syrups pruni serotini, liquid extract of liquorice.

With the advent of the newly discovered potent, specific chemotherapeutic and antibiotic drugs, dealing with the causes of cough, the infection, these old chemical and vegetable drugs, erstwhile almost sheet anchors of pulmonary diseases, have mostly lost their vaunted position, but nevertheless, as they are still sometimes used in selected conditions, as palliative adjuvants, a brief study of the important members and their basis of use, are included in the chapter.

Ipecac: The dried root of *Cephalis ipecacuanha*, contains 2% of total alkaloids, comprising, emetine (72%), cephalin (27%) and psychotrin (12%).

Preparations : (a) Pulv. ipecac — 30-120 mg. (b) Dover's powder (containing ipecac and opium) — 0.3—0.6 gm. (c) Tincture ipecac — 0.6—2 ml. (d) Emetine HCl. 30—60 mg. The *emetic dose* is 10 times greater.

Actions and Uses: (a) A mild irritant, reflex expectorant and emetic. (b) Dover's powder is a diaphoretic. (c) Emetine is used in acute amoebiasis but in large doses, it is a C.V. and C.N.S. depressant and can produce pulmonary congestion. It is hardly used in therapeutics excepting for amoebiasis.

Senega: The dried root of *Polygala senega* contains the glycosidal saponin-senegin.

Preparations : Tincture senega — 2-4 ml. It is an irritant for the G.I. tract and may produce dysentery like symptoms. The expectorant action is reflex from the stomach, which may stimulate bronchial secretions. It is now seldom used.

Tartar Emetic: Antimony and Potassium tartrate, in 1-3 mg. doses, is a nauseant expectorant, loosening tight cough. In 30 mg. doses, it is an emetic. It is a powerful depressant of heart and respiration and

may cause congestion of lungs. Because of toxicity, it is not used in therapeutics.

Iodides: K and Na iodides. *Dose:* 0.3-2 gms. The first is more frequently used than the second. They are eliminated through skin and mucous membrane, which they irritate, producing sneezing, lachrymation and oedema of eyelids and, glottis. The iodides liquify sputum and are used for *tight cough*. They also produce hyperaemia and excite glandular secretions during their excretion. They are not indicated in the acute stage of bronchitis and pneumonia, but in subacute and chronic conditions as well as in bronchial asthma and pleurisy. They help in the absorption of fluid. They are contra-indicated in pulmonary tuberculosis and may awaken a latent focus.

Ammonium Salts: The carbonate and chloride salts are used in doses of 0.3-2.0 gm. with codeine and a syrupy base. These are *reflex expectorants* irritating the stomach and rendering sputum less tenacious. They also stimulate the heart and circulation and are useful in acute and chronic bronchitis, when given in frequent doses. Their main use is in influenza, with early congestion and little expectoration.

Citrates and Acetates : Potassium, sodium and ammonium salts — 1-2 gm. given frequently with plenty of fluids, may liquify tenacious sputum and act as sedative expectorants. They also act as alkalisers and are used in fever cases.

Creosote, Guaiacol and Thiocol: The first is obtained from the beechwood tar and is a mixture of phenol. The second contains 90% of creosote and is very little soluble. *Dose:* 0.3—0.6 ml. Yellowish liquid with penetrating odour and taste. They are absorbed from the G.I. tract and excreted in urine and also from the lungs, which may be irritated.

They act as antiseptic, deodorant and stimulant expectorants in chronic bronchitis, bronchiectasis and gangrene of the lungs. In gastric fermentation, guaiacol — 1-2m. and in T.B., thiocol, is better tolerated.

Given as pillules or capsules, they sometimes wonderfully control secretions and reduce the foetor. They are never to be given in haemoptysis.

Benzoin and Benzoates: Gum benzoin or Sumtra benzoin, is a balsamic resin, containing benzoic and cinnamic acids, volatile oils and resins. *Dose:* Benzoic acid — 0.3—1 gm. Sod. benzoate — 0.3-2 gm.

Tinct. benzoin Co, *Friar's balsam*, containing 10% of gum benzoin, storax, balsam of tolu and alcohol, is used for inhalation purposes, in upper respiratory tract infections.

Tolutanum: Balsam of tolu is obtained by the incision of *Myroxylon toluifera* and is a tenacious, brownish, solid, aromatic substance which is soluble in alcohol. It contains cinnamic and benzoic acids. There are two important preparations — (a) Syrup — 2-8 ml. and (b) Tincture — 2-4 ml. It is an antiseptic, parasiticide and skin stimulant, used in bronchitis, as a mild expectorant. *Lozenges* may be used for sore throat and the *balsam* as a flavouring agent in cough mixtures.

Glycyrrhiza or Liquorice: Dried fruits of *Glycyrrhiza glabra* containing glycyrrhizin. (a) *Pulv. glycyrrhiza* contains liquorice and senna. *Dose:* 4-8 gm. and (b) *Liquid extract* 2-5 ml. It is a sialogogue, demulcent, mild purgative and is sometimes used as a *cough sedative* and also for the healing of peptic ulcer. It enters into the composition of many throat *lozenges* and *pastils*.

Of late, it has been found to possess glucocorticoid and anti-inflammatory effects and is being explored for use in rheumatoid arthritis.

Prunus Serotina: the bark of wild cherry contains a glycoside, enzyme, resin and hydrocyanic acid. *Syrup pruni serotini* — 2-8 ml. is mostly used as a *sedative expectorant* and also as a *flavouring* and *sweetening agent*, in cough mixtures.

THERAPUTIC CONSIDERATIONS

These drugs find their clinical uses in the following respiratory tract infections:

Acute Upper Respiratory Tract Infections: (a) Inhalation of Tr. benzoin Co., (b) Sulpha drugs and antibiotics, orally or parenterally, (c) Antihistaminics, particularly if the affections are allergic in nature.

Acute Tracheo-Bronchitis: (a) Inhalation of Tr. benzoin to 60 m./pint of steaming water. (b) During the acute phase, sedative linctus or Tinc camphor Co., and when expectoration starts, ammonium chloride, combined with squill and flavoured with syrup of tolu. (c) Suitable antibiotic therapy, as indicated by sputum, in suppurative bronchitis.

Pneumonia: (a) Sedative linctus to prevent early irritable and painful cough. In severe cases, morphine — 10 mg. may be needed.

(b) Kaolin poultice (antiphlogistine) and strapping are traditional measures and are particularly useful in relieving chest pain.

(c) Sulphonamide and antibiotic therapy — penicillin, streptocaine, and broad spectrum antibiotics, depending on the causative organism.

(d) Later on, ammon-carb and Tr. Ipecac may be given, if at all necessary, for promoting expectoration. Large doses of expectorants are however to be avoided because of their irritant action on the stomach.

Chronic Bronchitis: (a) Warm and equitable climate, is beneficial.

(b) If cough is troublesome and expectoration tenacious and scanty, various combinations of ammon. carb, Tr. ipecac, preps. of squill or senega, tolu, liquorice, prunii serotinii, may be given.

(c) In cases with bronchial spasm, antispasmodics — e.g. ephedrine stramonium, lobelia, belladonna or grindelia preparations, may be added to the expectorants.

(d) Anti-infective treatment with sulphonamides and antibiotics, depending on the causative organism. Treatment of rightsided failure and masking of offensive odour by creosote and other tar derivatives are also sometimes necessary.

Bronchiectasis: (a) Efficient emptying of the cavities by postural drainage, (b) Inhalation therapy of antibiotic depending on the organism in the sputum, (c) Use of ipecac, scilla, syr. tolu, ammon. carb, soda bicarb, as expectorant and finally, (d) Surgical resection of a segment or lobe, as indicated.

Whooping Cough: (a) *Prophylactic*: antipertussis vaccine and serum of the convalescent,

(b) *Specific therapy* with

(a) Chloromycetin — 200 mg/kg

(b) Streptomycin — 1 g.

(c) Polymyxin — 5 mg/kg or

(d) Terramycin — 125 mg/kg

and finally, (c) Palliative measures with pulmonary antispasmodics— Tr. belladonna and also use of sedative linctus, are the lines of treatment recommended.

CHAPTER

27

PHARMACOLOGY OF ANALGESIC-ANTIPYRETICS

ANTIRHEUMATIC, ANTIGOUT AND ANTIPYRETIC AGENTS. THEIR ACTIONS, TOXICITY, THERAPEUTIC USES AND LIMITATIONS

[A remarkable group of drugs which possess the unique properties of relieving myalgic, neuralgic and joint pains but unlike morphine, is ineffective in relieving visceral pains. These drugs also relieve inflammation and swelling of joints. Some of them also possess uricosuric effect and reduce body temperature in pyrexia. They do not possess addiction liabilities and are used in common cold, headache, arthritis gout and hyperpyrexia.

The *salicylate group* of drugs comprising sodium salicylate and aspirin, are household remedies for headaches and other body pains. The *colchicum-cinchophen group* comprising colchicine, cinchophen, associated with probenacid and ACTH, are used in gout while *butazolidine* along with *cortisone*, sodium salicylate, acetylsalicylic acid and some of the *gold* preparations, are used in *rheumatoid arthritis*. The salicylate therapy still remains the sheet anchor for acute rheumatic fever, producing cardiac complications if left untreated in the early stages.

Most of these drugs show *toxic* manifestations in prolonged therapy, salicylates producing salicylism, aspirin allergic manifestation, butazolidine—bone marrow depression and hepatitis, cinchophen-liver damage. The same remark applies to the *aniline-pyrozolone group* of antipyretics — acetanilid being toxic for blood causing methaemoglobinaemia and aminopyrine dangerous agranulocytosis.

Nevertheless, these analgesic-antipyretics have a definite place as useful therapeutic agents in a large number of common acute and chronic crippling conditions and along with other newer drugs, including corticoids, are popularly used in the therapy of (a) Acute rheumatic fever, (b) Ordinary arthritis and rheumatoid and other types of arthritis, (c) Gout and lithiasis, (d) Headache and migraine and (e) Undiagnosed threatening hyperpyrexia in children, in most of which, they have hardly any competition to excel over them.]

After the discovery of quinine, due to its shortage and cost, ceaseless efforts were made to find out synthetic substitutes, combining analgesic antipyretic and antimalarial properties. Though this last objective was not achieved, the newer compounds, thus synthesised, opened several important fields of actions by virtue of their analgesic, anti-inflammatory, uricosuric, antipyretic and other effects. Their analgesic action was found to be different from that of morphine and they were considered to belong to the group of *non-narcotic* analgesics.

The relief of pain produced by them referred more particularly to

neuralgic, myalgic and arthralgic pains, with or without inflammation or fever and the lowering of temperature, caused by them applied to any fever in which a general type of antipyretic action was desired.

Their analgesic and antipyretic actions were not fully dissociable and drugs belonging to different groups, showed varying degrees of overlapping of both the effects. These new drugs thus constituted a distinct group in itself different from the antimalarials and specific chemotherapeutic and antibiotic drugs, which also reduce pyrexia in specific infective conditions by dealing with the underlying causes of pyrexia. They are not therefore included in this chapter of *general analgesic-antipyretic agents*.

The *analgesic-antipyretics* comprise two principal groups of drugs:

- I. *Salicylate-Cinchophen group* — having predominantly analgesic antiinflammatory, uricosuric and also antipyretic action.
- II. *Aniline-Pyrozolone group* — possessing predominantly antipyretic but varying degrees of analgesic actions as well.

The *first* comprises the important subgroups of — (a) Salicylates, known for their antirheumatic and antiarthritic action and (b) Cinco-phenes reputed for uricosuric and antigout action.

The *second group* comprising aniline and pyrozolone derivatives of acetanilid, phenacetin, pyramintone and antipyretics of which are, the least toxic phenacetine is sometimes used in hyperpyrexia, along with aspirin, in the form of A.P.C. powder, for relief of myalgia and headache.

Besides these traditional analgesic-antipyretics, of late, several other drugs — corticoids, butazolidine, probenecid, chloroquin, also one or two gold preparations have been found efficacious in rheumatic and gouty conditions, as detailed hereafter.

CLASSIFICATION

Drugs used in Acute rheu- matic fever	Salicylates-Na salicylate, methyl salicylate, acetyl salicylic acid, gentisic acid- salicylamide, mephena- mic acid, chlorphen oxamine.	Drugs used in Rheuma- toid arthritis	Sodium salicylate, buta- zolidine, gold compounds, chloroquine, hydroxychloro- quine, ACTH and cortisone.
Drugs used in Gout	Colchicine, ACTH, corti- sone, cincophen, Na sali- cylate, aspirin, piperazine, probenecid	General Antipyretics	(a) Aniline derivatives-- acetanilid, phenacetin. (b) Pyrozolone derivative- antipyrene, amidopyrine Also acetylsalicylic acid.

Chemical structure of some of these compounds is shown in Plate XXIV. Fig. 63.

Plate XXIV

HEAT REGULATION AND ANTIPYRETIC DRUGS

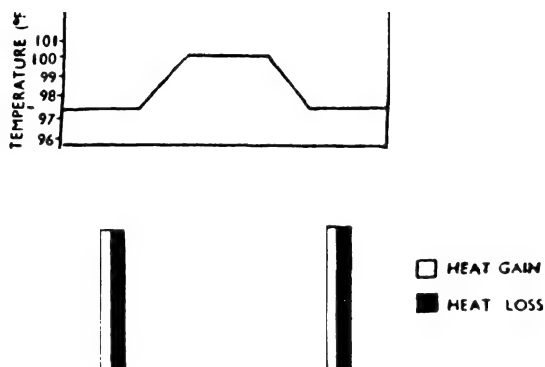


FIG. 62. Schematic diagram of stages of fever and disturbance in heat balance

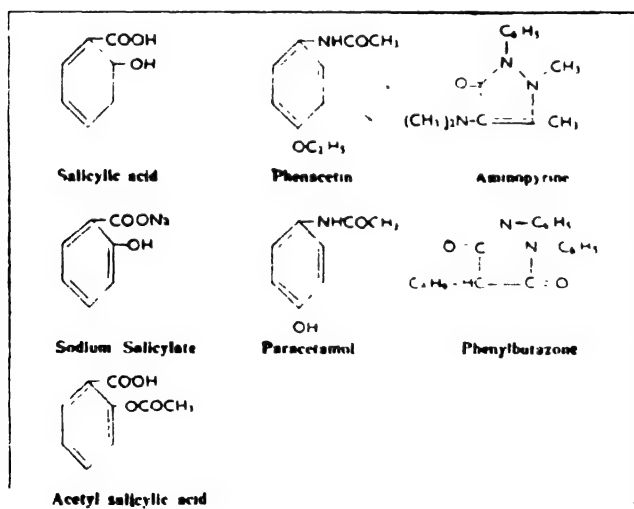
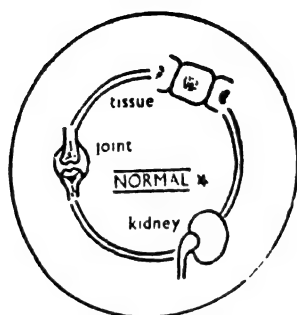


FIG. 63. Structural formulae of important analgesic antipyretic drugs.

Plate XXV

URIC ACID METABOLISM AND ANTIGOUT DRUGS

URIC ACID METABOLIC POOL



- uric acid produced by tissues
- carried by blood
- excreted by kidneys
- no deposition in joints

DRUG INCREASING URIC ACID MOBILISATION FROM THE JOINTS

- Colchicine

DRUGS EXERTING ANTI-INFLAMMATORY ACTION

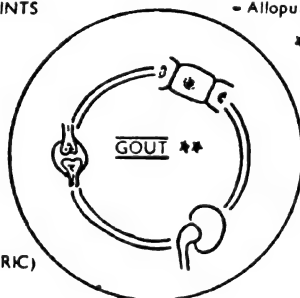
- Corticosteroids
- Salicylates

DRUGS INCREASING URIC ACID EXCRETION (URICOSURIC)

- Probenecid
- Salicylates
- Corticosteroids

DRUGS REDUCING URIC ACID PRODUCTION

- Allopurinol



- **
- increase in uric acid pool
- increased deposition in joints and soft tissues
- increase in blood

FIG. 64. Diagram showing uric acid metabolism in normal and gouty persons and the sites of action of antigout drugs.



FIG. 65
Colchicum autumnale.

ANALGESIC ANTIRHEUMATIC AGENTS

Pain is obliterated by general anaesthetics by producing a hiatus of unconsciousness and by morphine by raising the pain threshold by depression of the sensory cortex. The coal-tar analgesics of the present series, act on the sub-cortical level — (a) lateral spino-thalamic tract and (b) corpus striatum and thalamus, by raising the threshold of pain stimuli relayed from the thalamus to the cortex. These drugs therefore differ considerably from the opiates in respect of their analgesic action. Further, while morphine relieves deep-seated pains of visceral origin and of severe intensity, as in cancer and also produces addiction liabilities and a lot of after and side-effects, the salicylates relieve pains of moderate intensity, of myalgic and arthralgic nature, by acting on the subcortical level and without habit formation but some amount of tolerance and much less after-effects. Thus effects of these two groups of drugs are hardly comparable, each having its own specific applications.

Methods of Evaluation: In man, as well as, in animals.

- (a) Analgesiometry: the pain stimulus being thermal, mechanical, chemical, electrical, or pathological. The rise in threshold is accepted as proportional to analgesia.
- (b) Technique of radiant heat focussed on the forehead of man and sensation of pain provoked.
- (c) Ischaemic contraction method producing pain of specified intensity. In both these cases, drugs are given before and after and compared with known drugs.
- (d) Clinical evaluation in patients, suffering from malignancy.

SALICYLATES

These are derived from salicylic acid and comprise sodium salicylate, acetyl salicylic acid and methyl salicylate.

SALICYLIC ACID

A normal constituent of straw-berry and willow bark and is prepared from the interaction of sodium phenate and CO_2 . Light, feathery, sweetish crystals, sol. 1:500. *Dose:* 0.3–0.6 gm.

Action: It is absorbed through the skin and mucous membrane but is irritant. It circulates as sodium salicylate and is excreted as salicyluric

acid. It is a weak bacteriostatic, anhydrotic and keratolytic agent dissolving the horny layer of skin without provoking any pain.

Uses: (a) Antiseptic and food preservative. (b) Ung. acid salicylic—2% or *corn salves*—10-20% in acetone collodion, for corns and warts. (c) An anhydrotic powder and also used in ringworm.

METHYL SALICYLATE

Essence of Wintergreen is present in the oil of Gaultheria. It is an irritant rubefacient, counterirritant and anodyne. *Dose:* 0.3-1 ml.

Uses: Unguentum and liniment, used sometimes for rheumatic joints, sciatica and lumbago.

SODIUM SALICYLATE

It is prepared by the interaction of salicylic acid and NaHCO_3 or of sodium phenate + CO_2 . Odourless, fine needles, sweetish in taste and soluble in water. *Dose:* 0.6-2G. With ferric chloride it gives violet colour and with hydrochloric acid, salicylic acid. It is incompatible with antipyrine and renders caffeine soluble.

Metabolism: The drug is absorbed from the G.I. tract and a small portion hydrolysed to salicylic acid. Its distribution is rapid and uniform and no free salicylic acid is absorbed in the blood. Though excretion takes place by most of the channels—sweat, saliva, bile and faeces, the urinary excretion is the most important. It starts within 15 mins. attain a figure of 50% in 24 h. and traces upto the 3rd day. Aspirin and methyl salicylate are more slowly excreted. Sodium salicylate is partly conjugated as glycoronate sulphate and partly oxidised. Soda bicarb protects kidneys but does not hasten its excretion.

Action: (a) Local and (b) Systemic

Locally. A weak bacteriostatic and irritant for skin and mucous membrane. Action of salicylic acid is stronger than salicylates in this respect.

Systemic actions—very important and are as follows:

C.N.S.: Analgesic-antipyretic action from depression of optictalamus and hypothalamic thermostat and pain threshold is

increased by 35%. There is no inhibition of heat production but heat dissipation is increased.

C.V.S.: (a) Not depressed with therapeutic doses even by aspirin.

(b) In toxic doses, C.V. and V.M. depression.

G.I. Tract (a) Irritation and epigastric distress.

(b) Reputed choleric action but not confirmed experimentally.

Metabolism—Uric acid excretion is increased by 35-50% and renal threshold is considerably lowered. It is a uricosuric drug of some importance.

Blood—The alkali reserve is unaffected in therapeutic doses but in toxic doses, there is *acidosis* which is counteracted by soda bicarb. The *hypoprothrombinaemia* and *haemorrhagic tendencies* caused by the drug, are treated by the administration of *vitamin K*.

Urine—(a) Mild diuresis, probably by salt action. (b) In large doses, as in A.R.F., oliguria, albuminuria, nephritis and salicyl oedema.

Toxicology: Either from *idiosyncrasy*—skin rashes and anaphylactic condition or from *toxic doses* as in A.R.F., resembling cinchonism and known as *acute salicylism*. It is characterised by (a) nausea, vomiting, diarrhoea and profuse perspiration. (b) headache, dizziness, tinnitus, dim vision and confusion. (c) C.V. and respiratory depression, asphyxia stupor and death. (d) also haemorrhagic tendencies.

Treatment: Mostly symptomatic—(a) lavage of stomach and magnesium sulphate as a purgative, (b) liberal fluid and glucose saline, (c) adrenaline for allergic manifestations and (d) vitamin K for hypoprothrombi-naemia.

Mechanism of Action: The remarkable action of salicylates in A.R.F. and also some effect in gout, has in the past been ascribed to its analgesic-antipyretic effect, known for a long time. Both these conditions are associated with pain, inflammation, swelling and fever and in the latter, also disturbances in purine metabolism.

There is no doubt that the analgesic-antipyretic actions of salicylates are of importance but more light has been thrown on other mechanisms as well, in recent years, which are as follows:

1. *Inhibition of hyaluronidase.* Hyaluronic acid is the binding factor for connective tissue fibres and this is disintegrated by the enzyme hyaluronidase or the spreading factor, which is increased in A.R.F.

The inhibitory action of salicylates on this enzyme brings about amelioration and relief.

2. *Inhibition of fibrinolysin.* It is a proteolytic enzyme which acts on the fibrin. Some of its breakdown products cause widespread inflammatory reactions. By inhibiting fibrinolysin, salutary results are produced by the salicylates.

3. *Chelation.* A new terminology, which is utilised for explaining the specific actions of a number of substances. The word means *clawing* or *grabbing of metals*. Chelation is done by 'O of COOH and O as of OH' and it occurs better if COOH and OH groups are close and in ortho position. Antirheumatic properties of salicylates have been ascribed to its chelating properties.

4. *Uricosuric action.* This refers particularly to gout, in which the threshold for excretion of this end-product of protein metabolism is lowered, resulting in the free excretion of uric acid and consequent amelioration of gout.

The mechanisms detailed in (1) and (3) also apply to cortisone, which is effectively used in the treatment of acute rheumatic fever.

Uses: Several; some for common conditions and others as more specific therapy.

Common uses.

(a) Sclerosing agent in varicose veins: 20-40%: 5 ml., injected into the affected vein.

(b) Analgesic—antipyretic in common cold and influenza associated with myalgia.

(c) In gout as analgesic, anti-inflammatory and uricosuric.

(d) Acute intra-ocular inflammations for the relief of pain.

Major use. 'Salicylate therapy' is still a sheet anchor in the treatment of A.R.F., characterised by (a) hyperpyrexia, (b) fleeting arthritis, involving the big joints, (c) profuse perspiration, (d) rashes, and (e) cardiac complications.

For such a crippling disease, in children and young adults, three essential points for effective therapy are (a) early diagnosis, (b) early treatment and (c) use of optimal dose level.

Sodium salicylate. 10-12 gm/day/ in three hourly doses, till the effective blood concentration of 35-40 mg% is attained. This concentration is then maintained till symptoms abate and E.S.R. comes back to the normal. With proper treatment, cardiac complications are prevented

in 80% of cases. If, however, the treatment is prematurely stopped or less doses are used, there is a recrudescence and the patient heads towards the mitral lesions, which once set in, are unaffected by salicylate therapy. With an ideal therapy, improvement is expected in the majority of cases and real failures are only in 5-10%, which further improve if *cortisone therapy* is associated with it.

Gentisic Acid: A dihydrobenzoic acid derivative and a normal urinary metabolite during salicylate therapy, it was introduced in 1948, because of its antihyaluronidase activity which effect has not yet been fully confirmed. The compound is readily metabolised reaching peak level in 2 hours. Probenecid and methyl cellulose slow down its renal excretion and intestinal absorption respectively. *Dose:* 5-20 gm/day/ in 3 hourly doses for 10 days. Though less toxic than salicylates, it is in no way superior to the latter. **Salicylamides:** 2-hydroxy benzamine, a white, sparingly soluble, crystalline powder, resembling sodium salicylate in metabolism and action. It is used in doses of 2 gm./ 3-6 times/ day and is less toxic. **Sodium gamma-resorcinilate:** It is 10 times more potent and much more toxic. It is given in 1 gm. daily, divided doses. It suppresses inflammatory reactions and delays the healing of wounds, like ACTH and Cortisone. The drug is capable of producing 'emotional instability' and Cushing's syndrome.

ACETYL SALICYLIC ACID

Commonly known as *aspirin* or *aspro*, it was introduced by Derser in Medicine with the idea that it would be absorbed from the intestine and cause no liberation of salicylic acid in the stomach, as is the case with sodium salicylate. This has not been achieved. It is a white, insoluble powder, dispensed as tablets of 0.3 gm. each. *Dose.* 0.3-0.6 gm.

- Action:**
- (a) It is partially hydrolysed in the stomach and absorbed from the intestine.
 - (b) It is $1\frac{1}{4}$ times more toxic than sodium salicylate.
 - (c) It is probably a better analgesic for neuralgic types of pain, headache, myalgia of common cold, influenza, tabetic crisis etc.
 - (d) It is one of the most widely used and abused drugs, by the lay public.
 - (e) On prolonged use, it may give hyperchlorhydria and peptic ulcer.
 - (f) Contrary to the popular belief, it is not a depressant for the heart in therapeutic doses unless grossly abused or there is idiosyncrasy.

Toxicity: (a) G.I. irritation, (b) alarming allergy-urticaria, tachycardia sometimes, which is treated by calcium gluconate, adrenaline and antihistaminics.

Uses: (a) relief of pain, (b) rheumatic fever, (c) gout, (d) migraine, (e) dysmenorrhoea, (f) common cold and flu, (g) tabetic crisis.

PHENYL BUTAZONE OR BUTAZOLIDIN

Popularly known as Irgapyrin: It is an antiinflammatory and antipyretic drug, which has come into wide therapeutic use in recent years. *Chemically*, it is a pyrazole derivative, which finds its application in a large number of conditions — acute rheumatic pain, rheumatoid arthritis, osteo-arthritis etc.

Actions: Resembles amidopyrine; (a) depression of heat and pain centres, (b) antidiuretic action, (c) antihistaminic action; all probably mediated through the hypothalamus.

Toxicity: Epigastric pain, vomiting, diarrhoea, headache, agranulocytosis and hepatitis, in some cases.

For relieving rheumatic pains, the blood level of the drug should be 8-10 mg%, and to be maintained at 4-8 mg.%. Toxic level starts from 10 mg%. The safety margin is thus comparatively low. *Dose:* 200 mg. daily, in enteric coated tablets. Usual dose 100-400 mg/day. The drug also lowers blood uric acid level, diminishes tubular reabsorption of uric acid in 400-1000 mg. doses.

Chlorthenoxazen. It has properties similar to the salicylates but has longer duration of action, as well as, muscle relaxant activity. It is converted in the body to gentisic acid which may be responsible for its action. Its antiinflammatory action resembles corticosteroids but it is less toxic. Its main indication is in chronic pain with muscles spasm.

Mefenamic Acid. A newer analgesic with antipyretic and anti-inflammatory actions, which resembles aspirin but is more potent on the weight basis.

ACTH AND CORTICOSTEROIDS

These newer hormones, obtained from the anterior pituitary (ACTH) and supearenal cortex, respectively, have been ascribed to many striking pharmacological actions — anti-inflammatory, uricosuric

and antiallergic. The glucocorticoids-cortisone, prednisone, prednisolone, find their uses in collagen disorders (rheumatoid arthritis, rheumatic fever and gout) and also in acute stages of many other diseases. They are supposed to increase body resistance and immunity in diseases.

In rheumatoid arthritis, they provide symptomatic relief, reduce pain, swelling and inflammation, increase the range of movement and also the strength of joints and limbs, but when the administration is ceased, the symptoms reappear and there is no clinical cure. They are used only when other drugs are ineffective. In acute rheumatic fever also, the corticoids are used with no special advantages over the salicylates.

GOLD COMPOUNDS

Various preparations of gold have been in medicinal use during all these centuries but like the triumphal chariot of anatomy, they have been accepted and discarded successively, due principally to inefficacy and toxicity. Its use in the exudative type of tuberculosis, lupus vulgaris and many other conditions has almost been discarded, but it is still sometimes used in the treatment of rheumatoid arthritis.

Preparations: (a) Sodium aurothiomalate-myocrysin-graded doses of 10-20-50-100-200 mg/8-10 I.M. Injection. (b) Auri et Na thiosulphas-sanocrysin: snow white crystals. Dose: 10-25-50-100-250-500 mg. I.V. every 5th/7th day. Total dose-4-5 gm. (c) Aurothioglucose (*Solgenal*).

Of these, myocrysin is mostly used. The gold preparations are very little absorbed through the gut and after parenteral use, 80% is excreted through the urine and the rest through the faeces.

Toxicology: (a) *Immediate*-malaise, headache, giddiness, angioneurotic oedema, vomiting, diarrhoea and colic pain.

(b) Toxic nephritis, hepatitis, urticaria, exfoliative dermatitis, generalised pigmentation.

(c) Malignant thrombocytopaenia, agranulocytosis, aplastic anaemia and peripheral neuritis.

During gold therapy, it is necessary to get the urine tested regularly and the face protected from sunlight for avoiding violet discoloration.

Treatment. Ca gluconate, Na thiosulphate and BAL.

ANTIGOUT DRUGS

Gout is a metabolic disease in which there is a deposition of uric acid and urates in small joints starting often with metatarsal-phalangeal joint of the great toe and the surrounding tissues forming what is known as *tophi*. Inflammatory reactions along with painful swelling of the joints occur, resulting in acute gout, which if untreated, passes on to the chronic form, with periodical exacerbations of an acute nature.

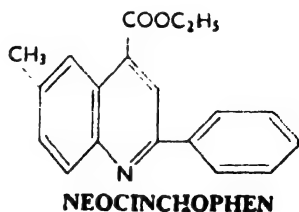
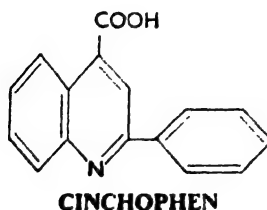
Uric acid is formed by the breakdown of purines and also by direct synthesis from glycine. It is excreted as uric acid, in urine, in man but in certain mammals after being oxidised to allantoin. The normal blood uric acid level in man is between 2-3.5 mg/100 ml. In the kidney, much of the filtered uric acid is reabsorbed, the 24 hours excretion being 0.5 to 1 gm.

In primary gout, uric acid produced from glycine is increased and blood uric acid level is increased, because of the decrease in the renal uric excretion. In secondary gout, the uric acid level in the body is elevated, secondary to the excessive breakdown of nucleic acid, as in leukaemia and pneumonia, or secondary to increased nucleic acid turn-over, as in polycythaemia. In starvation also, blood uric acid level is increased, probably because of increased nucleic acid breakdown.

Increase of uric acid is also sometimes associated with decreased adrenocortical functions. Hence gout can be treated by (i) increasing uric acid excretion by uricosuric drugs for chronic gout, (ii) decreasing uric acid synthesis or (iii) improving adreno-cortical functions. Drugs like colchicine, improve gout by mechanisms not known. (Plate XXV—Fig. 62).

CINCHOPHEN

Also known as *atophan*, it is a yellowish powder, insoluble but soluble in the presence of alkali and sodium salicylate. *Dose*: 0.3-0.6 gm.



Illus. XV. Structural differences between Cinchophen and Neocinchophen

Metabolism: The drug is slowly absorbed through the G.I. tract but more easily from the S.C. tissues. Its sojourn is not clearly known. It is excreted as it is or as *oxytophan*.

Action: It resembles sodium salicylate and aspirin in many respects and is an (a) analgesic (b) antipyretic (c) choleretic (d) antiphlogestic and (e) antigout remedy.

It brings down the body temperature by peripheral vasodilatation and diaphoresis. The antiphlogestic action is demonstrable experimentally on rabbit cornea against mustard irritation and its choleretic action is superior to that of salicylates but the chologogue effect is less important.

Uricosuric Action. It has a selective action on the uric acid metabolism, which is formed from the improper oxidation of purines of food.

The drug may increase the destruction of nucleoproteins, mobilise uric acid from the tophi gouty deposits and tissues, decrease the blood uric acid and N.P.N., lower the renal threshold for excretion of uric acid and thus increase its excretion. The creatinine content of blood, however, remains unchanged.

The above actions are more marked during the acute attacks of gout. The action is of very temporary nature and blood uric level returns to the previous levels immediately after the cessation of treatment. Majority of authorities however doubt its real efficacy and because of its serious hepatotoxicity, it is very seldom used, these days.

Toxicology: (a) Gastrointestinal irritation, nausea, vomiting and diarrhoea. The drug has produced gastric ulcers in dogs. (b) Liver damage and even acute atrophy of the liver, following hepatitis, which is rather a serious manifestation of its toxicity.

Uses: Not much used in acute gout and because of toxicity, its uricosuric action is not exploited in chronic gout. If used, it has to be done with caution, along with soda bicarb, for flushing the kidneys.

Neocinchophen: Pale-yellow powder, odourless, tasteless and nearly insoluble in H_2O . **Dose:** 0.2-0.3 gm. 4-6 times daily. It is less toxic than cinchophen and is a better palliative in acute attacks. Its toxicity is of the same type as of salicylates and atophan but the frequency is much less.

COLCHICUM

The bulbs and seeds of *Colchicum autumnale* (Plate XXV: Fig. 65), containing colchicine are used. The alkaloid is a white powder, oxidising to yellow oxycolchicine and is bitter and soluble.

Preparations. Dry extract, powder and liq. extract, are of very little use. *Tincture*: 0.3-1.0 ml and the alkaloid, *colchicine* and demicolchicine—1/2 mg./hr, till relief ensues, are the only preparations of importance and use.

Action: The drug has a rapid absorption but slow action and excretion. It produces a cumulative action. *Oxydicolchicine* is the active form in the body.

Antigout Action. It has no action on the uric acid metabolism, experimentally there is no analgesic-antipyretic action, but still there is *dramatic relief* in acute gout, though the basis of action is still unknown. Being a nucleotoxic drug, it may affect the mitosis of cells and produce mutation.

Toxicity: (a) A typical picture of acute gastro enteritis with purging, vomiting, thirst, foetid, haemorrhagic stool, tenesmus. The action resembles pilocarpine but may be due to some simple irritation of the G.I. tract.

(b) Sometimes renal damage and ascending paralysis have been observed. Gout starts improving when diarrhoea sets in.

Treatment. Comprises administering drugs like demulcents, tannic acid, atropine and elixir paragoric.

Uses: It is almost the drug of choice for acute exacerbations of gout. It is to be given in full doses of 1-2 mg. every 2 hrs for 2-3 days. The bowels should be kept open. It is a very good palliative in the majority of cases but the mechanism of action is not understood.

Demicolchicine: or Des acetyl methyl colchicine is a synthetic derivative of colchicine and useful in acute gout. *Dose:* 5 mg initially, followed by 1 mg hourly/3 doses. It is relatively free from G.I. irritation produced by colchicine.

Probenecid: or Benomid or Caronamide is a benzoic acid derivative which inhibits renal tubular transport of organic acids. The therapeutic applications are limited to the modification of excretion of penicillin, and uric acid. When given in adequate concentrations,

it prevents excretion of penicillin. Its use in gout is based upon the fact that it prevents the reabsorption of uric acid by renal tubules and increases excretion of uric acid.

The acute attacks of gout are not affected by the drug, on the contrary, during the earlier period of treatment with probenecid, the frequency and severity of attacks may increase, for which, colchicine, in doses of 0.5—2 mg/day, may be added. During probenecid therapy, salicylates should not be used, because of their antagonistic action.

For the treatment of chronic gout, probenecid therapy should be given continuously, initially a single dose of 0.5 gm/day for 1 week., followed by 0.5 gm twice daily.

Toxicity: Gastrointestinal irritation, skin rashes, formation of stones, stimulation of C.N.S., convulsions, respiratory failure, drug fever and renal colic.

ACTH and Cortisone: These two hormones, as detailed in their respective chapters, are important addition in modern therapeutics. ACTH, as the name suggests, is the adrenocorticotrophic hormone of the anterior pituitary body and cortisone is an adreno-corticoid. ACTH acts by stimulating the secretion of corticoids. They have uricosuric and anti-inflammatory actions in gout and ACTH is often used along with colchicine, in the long term therapy of gout. Stopping of the drug may precipitate an attack and consequently, colchicine therapy has to be associated with this drug and even continued for a few days after ACTH has been stopped. Further, its dose has to be tapered off.

Piperazine: An old drug with alleged uricosuric and stone dissolving reputation, used sometimes, in doses of 0.3—1 gm t.d.s. in chronic gout, lithiasis, uric acid diathesis and recently also in worm infestations.

Drugs like DON which decrease the synthesis of uric acid, intravenous glucose, hexamine and diodone are of theoretical interest only.

Zoxazolamine. A new chemical compound producing skeletal muscle relaxation. It acts by selective depression of transmission through the subcortical brain stem and polysynaptic pathways. It has better action (amelioration in about 90 % cases) in rheumatoid arthritis, spinal spasticity and parkinson's disease and has also potent uricosuric action, similar to probenecid. However, because of toxicity, the drug has been withdrawn from market.

THERAPEUTIC SPECTRUM

Major: Colchicine ACTH cortisone, butazolidine	Major: Sodium salicylate, aspirin, probenecid.
ACUTE Others: Salicylates, cinchophen, 3-hydroxy-2-phenyl cinchoninic acid (HPC), intravenous heparin.	CHRONIC Others: ACTH and cortisone, ethyl biscoumacetate, piperazine, Zoxazolamine.

GENERAL OR TRUE ANTIPYRETICS

They comprise : (1) *Aniline derivatives*—acetanilid, phenacetin, (2) *Pyrazolone derivatives*—antipyrine, pyramidon. Their chemical structures are shown in Plate XXIV; Fig. 63.

They are primarily antipyretic, moderately analgesic and indicated in hyperpyrexia but are not specific for acute rheumatic fever and gout.

General Considerations: (a) The heat regulating centre is in the hypothalamus. Its stimulation produces hyperpyrexia and depression, subnormal temperature. (b) Application of ice on the carotid sinus produces shivering and application of heat, the opposite effect. (c) In *poikilotherms*, there are great variations in the body temperature, which is not the case with the *homoeotherms*.

Temperature Regulation: This is effected in the following manner:

(a) When the temperature is at 37°C, the temperature at the centre and the periphery is at equilibrium.

(b) When an infection has occurred, the centre is first set up at a higher gear, say 40°C, the blood passing through it from the periphery being still at 37°C, the shivering or the chill stage for conservation of heat and equalisation of temperature at the centre and periphery occurs, through vasoconstriction, less radiation and more heat production, when finally, central and peripheral temperatures become the same, that is the *heat stage*.

(c) Thereafter, when the cause of pyrexia is held in abeyance, the central temperature comes down to the normal of 37°C, while the peripheral temperature still remains high at 40°C. Blood passing through the centre, gives the sensation of heat. Consequently, there is vasodilatation, perspiration and heat loss, till the equilibrium is uniformly attained at 37°C in the centre and the periphery. This is known as the *sweat stage*. (Plate XXIV; Fig. 62).

This heat regulation is thus affected by heat conservation and heat loss, through different channels and mostly, the skin and the lungs.

Experimental Hyperpyrexia: This can be induced by:

- (a) Antigens — pyrogens, TAB vaccine and milk.
- (b) Drugs and chemicals—belladonna, cocaine, colloidal metals, dinitrophenol.
- (c) Inoculation of malarial infection.
- (d) Use of Electric blanket, heat puncture.
- (e) Some of these are used for evaluation of antipyretics and others for pyretic therapy in the treatment of G.P.I., rheumatoid arthritis and chronic salpingitis.

The actual method of study consists of the determination of rectal temperature and skin thermometry in rabbits.

General Characteristics: (a) Actions of most of the antipyretics are rapid, short lasting and more marked in hyperpyrexia. (b) Though they act centrally, their action is mediated peripherally through vasodilatation. (c) Most of them, excepting phenacetin, are toxic for skin and blood. (d) Further, due to their analgesic action, as well as, cerebral vasodilatation, they cause a mild degree of dulling of the sensation, in most of the patients.

ANILINE DERIVATIVES

Though these were the innovators of *Farben industry* and *drug synthesis*, they are toxic and rather than of pharmacological importance, any more.

ACETANILID

A coal tar derivative, prepared by the interaction of aniline and acetic acid. White crystalline, pungent powder. Sol. 1:210 Dose: 0.3 gm.

It is rapidly absorbed from the G.I. tract, converted to p-aminophenol and excreted in urine after conjugation. It has a predominant analgesic-antipyretic action, the former being even stronger than that of aspirin. The *toxic* effects comprise cyanosis, methaemoglobinaemia, diminished activity of hearing, cardiac depression, vomiting and collapse. Because of toxicity, it has hardly any use in therapeutics.

PHENACETIN

Also known as acetophenetidine, it is a p-aminophenol derivative. White crystalline powder. Sol. 1:1700. *Dose*: 0.3-0.6 gm.

Metabolism: Its absorption is somewhat slow and takes about 2 hours. It is conjugated and then excreted in urine as p-aminophenol.

Action: (a) An analgesic and antipyretic drug of importance but due to the presence of the ethoxy group, its toxicity and antipyretic effects are somewhat less than with others. (b) It is a drug with insignificant cardiac depression. (c) Acuity of hearing is increased.

Uses: A.P.C. powder—containing aspirin, phenacetin and caffeine or codeine, is a cheap and effective combination for headache, myalgia and flu and routinely used. In small doses of 60 mg, it acts as a hypnotic for children.

PYROZOLON DERIVATIVES

Antipyrine or phenazone and pyramidon or amidopyrine are the important compounds.

PHENAZONE OR ANTIPYRINE

White, bitter powder, sol. in 1:1.2: *Dose*: 0.3-0.6 gm. It has a wide range of incompatibilities—tannin, chloral hydrate, salicylates and iron. It is better given alone. It increases solubility of quinine and caffeine.

Action and Uses: The drug is quickly absorbed and excreted as oxyantipyrine. It has a strong antipyretic and analgesic action and in 10% solution, it acts as a haemostatic in epistaxis. It is, however, less frequently used than phenacetin. Its toxic symptoms are erythema and burning in the stomach, hyperreflexia and cardiac depression. But on the whole, its toxicity is much less than that of acetanilid and amidopyrine.

AMIDOPYRINE OR PYRAMIDON

White, crystalline powder, sol. 1:18, *Dose*: 0.1-0.3 gm. Cibalgine, allonal and veramon are some of the combinations of this drug with others, for better analgesic effect.

Actions: (a) It is rapidly absorbed, conjugated in liver and excreted as rebasonic acid. (b) It has the strongest and longest antipyretic action and equivalent analgesic action with salicylates, but worst toxicity—(i) G.I. distress, (ii) skin rashes, (iii) C.V. depression and (iv) methaemoglobinaemia, though rare but in worst form. (v) Finally, it is notorious for provoking agranulocytosis, for which (a) blood transfusion, (b) penicillin (c) pentnucleotide 0.7 g./10 ml I.M. b.i.d. or t.i.d. for 5 days then once daily till normal blood picture is reinstated, and finally, folic acid therapy are indicated. With the above modes of treatment, the mortality rate has been reduced from 75% to less than 38% now.

In substance. The salient points in respect of the members of the general antipyretics are: (a) Minimum solubility of the aniline group, (b) blood dyscrasia and C.V. depression of acetanilid, (c) Bone marrow depression and agranulocytosis, produced by amidopyrine, (d) Skin disorders of erythema type and haemostatic effect produced by anti-pyrine and (e) Safety combined with efficacy of phenacetin, are the important features of these drugs.

THERAPEUTIC CONSIDERATIONS

The analgesic-antipyretics find a number of important uses. Besides, what have been indicated against the respective members, the important uses in the actual therapy of diseases, are detailed below:

Acute Rheumatic Fever: This condition may either be a streptococcal infection or an allergic disorder. Besides general management with complete rest in bed and application of heat to the affected joints, the standard treatment comprises the following:

(a) *Sodium salicylate*, 1.3-2.0 gm every 3 hours, totalling to 10-12 gm per day for adults and 4-8 gm per day for children. Sodium bicarbonate, in half the above quantity, should be simultaneously administered. If the oral salicylate therapy is not tolerated, 1.0 gm of sodium salicylate in conjunction with 3.0 gm of glucose should be given intravenously. *Aspirin*, 8.0 gm with calcium succinate, 6.0 gm, may also be tried in such cases. (b) ACTH, cortisone, gentisic acid, salicylamide, irgapyrine may be used in cases not responding adequately to the salicylate therapy. (c) *Codeine phosphate*, 30.0 mg t.d.s., pheno-barbitone, 15-30 mg, t.d.s., vitamin C, 500 mg and vitamin K, 5-10 mg, may have to be given as adjuvants, as well as, for preventing the toxicity of salicylates. Although initial improvement seems to be

greater with cortisone, compared with salicylate therapy alone, the long-term effects are the same in both the cases.

Rheumatoid Arthritis: This is a painful condition of unknown etiology, involving the smaller joints commonly. The onset may be acute or insidious and there is swelling of joints, fever, slight leucocytosis, sweating, anaemia and wasting of the muscles in the proximity of the joints. If unchecked, the joints are progressively damaged leading to stiffness and fibrosis. The treatment therefore should be planned on the basis of the stage of the disease.

In the *acute stage*, besides rest to the joint, application of heat and eradication of the septic focus, drug therapy for the suppression of the pain and inflammation, comprises the judicious use of the following:

(a) *Aspirin*. The simplest of all the remedies, which should be given a trial, particularly, in less severe cases. Average optimum daily dose is 4-6 gm., though this dose may not be tolerated by some patients.

(b) *Butazolidine*. A powerful but more toxic analgesic, which steps in when aspirin fails. It is claimed to be a specific antirheumatoid agent and is given initially in divided doses of 0.2 gm./day. This may be increased by 0.1 gm daily, to a maximum of 0.6 gm/day. If no improvement is observed in a week, it should be discontinued. During butazolidine therapy, haematological check up and vigilance over toxic manifestations, are necessary.

(c) *Gold*. It is recommended when the above analgesics have all failed. Gold, if effective, is so only during the first course. The preparation of choice is *myocrisin*, which is initially given in a dose of 10-20 mg./weekly and subsequently increased to 50 or 100 mg. Administration of a total dose of 1 gm., constitutes a single course. 3-4 such courses may be repeated at 8 weeks intervals. Toxic effects like albuminuria, bone-marrow depressions and dermatitis, should be watched.

(d) *ACTH and Cortisone*. Their long term effects are not much superior to those of the other drugs. The special advantages are that the remissions occur faster and last longer. Cortisone has a disadvantage over ACTH, in that it cannot be given for a long period, as it causes a depression of adrenal cortical functions. ACTH is initially given in a dose of 40 units I.M. If the response is satisfactory, the dose is gradually reduced by 5 units, every 2-3 days, until a maintenance level is found. *Prednisolone* is the steroid of choice. The initial dose of 10-15 mg./day, is cautiously increased till a satisfactory response is

obtained. The dose is then reduced to a minimal maintenance level. Prednisolone should not be withdrawn abruptly and the dose should be tapered gradually during withdrawal. Its toxicity includes increased gastric acidity, oedema, moderate hypertension and mild Cushing's syndrome. *Steroid therapy* is specially indicated in patients under 50 years of age with progressive damage to the joints and who for socio-economic reasons, cannot undergo prolonged therapy. It is also indicated in patients refractory to other forms of treatment.

(e) *Chloroquin*, hydroxychloroquin and zoxazolamine are the other drugs which have been found to afford symptomatic relief, sometimes, but because of toxicity and other considerations the last particularly has almost been discarded now.

(f) *Injections of milk*, *TAB vaccine* etc which cause a nonspecific protein reaction, adequate vitamins, iron and proteins, should be supplemented to counteract anaemia and muscular wasting. Similarly, thyroid therapy, Dover's powder and codeine may sometimes be recommended. The role of local use of hydrocortisone, physiotherapy, massage and surgical interventions, in cases of permanent chronic disability from ankylosis, is also important.

Gout: The management of gout involves not only the correction of uric acid metabolism, which in this case, is formed in excess from simple carbon and nitrogen compounds without intermediary incorporation in nucleic acid and consequent increase in diffusible and non-diffusible uric acid in the body. Several other factors like corticoid deficiencies, infections, inflammations and also pain, are also to be duly dealt with. The *general measures* of treatment include, bed rest, kaolin poultice, infra red and short wave diathermy, calomel and saline purgatives and also lactovegetarian diet during the acute attacks.

Drug therapy during *acute attacks* comprises the use of (a) Tincture colchicum-1 ml. or colchicine 1 mg. or demecolchicin 5 mg., initially and then hourly until relief of pain or onset of diarrhoea occurs. (b) ACTH or cortisone, particularly the former, in doses of 20 units I.M. along with colchicine 0.5 mg., offers the best result. (c) Cinchophen and phenylbutazone may be tried in certain cases and (d) for *chronic gout*, probenecid, piperazine, sodium salicylate or aspirin, may also be tried. Though the disease is intricate, planned therapy offers good results and even permanent cure in more than 90% of the cases.

Hyperpyrexia: The temperature regulating centre, under certain situations e.g. exposure to heat, infections, pontine haemorrhage, gets

disturbed, resulting in an acute rise of body temperature above 105°F. This occurs chiefly from vasoconstriction and absence of sweating, both these factors preventing the heat loss.

The chief effects of hyperpyrexia are reflected upon the central nervous system and coma, congestion of brain and haemorrhages, may occur. The cardiovascular system may be affected, resulting in cardiac and circulatory failures.

Treatment is aimed at bringing down the body temperature to at least 103°F in a controlled manner. This can be done by increasing the heat loss from the body. The measures used are: (a) Application of ice pads or wet sheets on the body. Sometimes the body may be immersed in cold water (b) Vasodilatation and sweating can be induced by the administration of the antipyretic drugs like phenacetin, aspirin etc or hypodermic drugs like chlorpromazine. These drugs should be used with great caution in children, as sometimes, even small doses of aspirin may reduce the temperature, very considerably.

While these measures are being applied, frequent monitoring of the rectal temperature has to be done ensuring that it does not go below 102°F, in any case. Any precipitous fall of temperature should be avoided. In cases where electrolyte imbalance and sodium loss have occurred, it should be made good by the administration of rectal or I.V. saline.

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SECTION
VI
CARDIOVASCULAR SYSTEM, BLOOD AND
BLOOD FORMING ORGANS

CHAPTER

28

GENERAL CONSIDERATIONS

PROPERTIES OF CARDIAC MUSCLE. AUTONOMIC CONTROL OF HEART
AND BLOOD VESSELS. CARDIAC RESERVE. ARRHYTHMIA AND HEART
FAILURE

[The pharmacology of the C.V. system presupposes an appropriate understanding of the physiology of heart, coronary vessels and circulation.

Essential properties of cardiac muscle comprise contractility, excitability, conductivity, tonicity and also abnormal type of excitability. The heart muscle obeys the laws of *all or none* in respect of responses to excitation and also of *Starling*, in respect of force of contraction. It cannot run into oxygen debt and must be assured of adequate blood supply, rate and volume of blood pumped and peripheral resistance. The amplitude and the rate of contraction are controlled by the tone of the heart muscle through antagonistically acting sympathetic and parasympathetic nerves. The heart normally has adequate reserve but when this is depressed or exhausted from increased work load, malnutrition and pathological conditions, cardiac failure gradually ensues, passing through the stages of *compensated* and *decompensated* heart.

Normal blood pressure depends on the cardiac output, peripheral resistance, viscosity and volume of blood and also elasticity of blood vessels, regulated by vaso-constrictor and dilator fibres, under the control of the V.M. Centre.

When the normal orderly sequence of contraction of different chambers of the heart is impaired from disturbances in the S.A. and A.V. nodes and the conduction system, cardiac arrhythmia occurs, resulting in fibrillation, flutter, paroxysmal tachycardia and partial or complete heart block. All these eventually lead to left or right-sided cardiac failure and death.

Effective drugs for correction and improvement of these disorders are available as curative and palliative measures and with advanced, ingenious techniques, experimental cardiac disorders can be produced for assessing drug effects, in these conditions, permitting the discovery of newer C. V. drugs.]

A section of paramount importance, comprising chapters dealing with drugs acting on the heart, circulation, coronary vessels, and also

Plate XXVI

PHYSIOLOGY OF HEART AND GENESIS OF ATRIAL FIBRILLATION

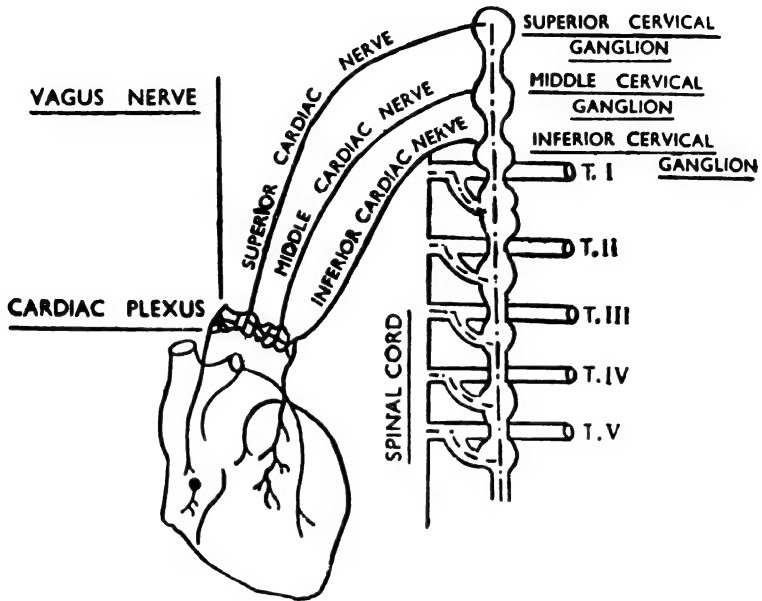


FIG. 66 Autonomic control of heart

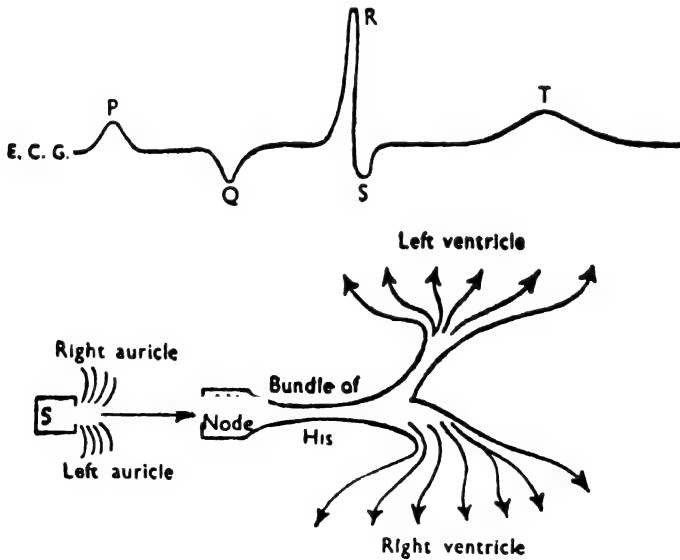
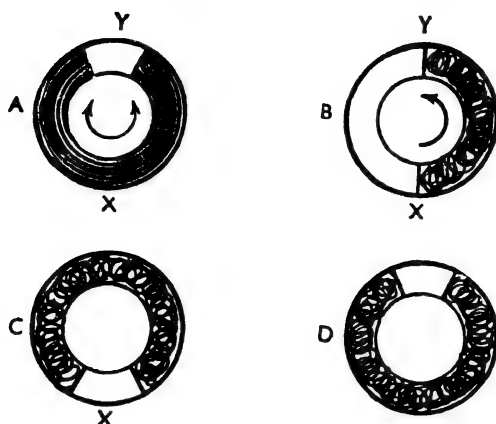


FIG. 67 Spread of excitation in heart muscle and junctional tissue (lower panel) and corresponding electrocardiogram (upper panel)

Plate XXVI—Contd.**FIG. 68** *Circus movement in auricular fibrillation:*

(The diagrams depict a ring of myocardium)

(A) When a portion of myocardium (X) is stimulated, waves of excitation travel in all directions and leave the excited muscle behind in a refractive state. The waves ultimately meet and cancel each other at (Y).

(B) If due to any reason the impulse is allowed to travel preferentially in one direction, then it goes around (Y) and

(C) Returns to (X).

(D) If the conduction velocity of the impulse through the myocardium is slow, then the impulse will reach (X) after the myocardium there has regained its excitability and the impulse will go beyond (X) and travel round and round the ring, constituting a circus movement. This will result in arrhythmia.

(Drugs slowing conduction will favour circus movement whereas drugs prolonging the refractory period will stop the impulse at 'X' and arrest the circus movement).

the haemopoietic system. The present chapter refers to the general physio-pathological considerations.

Physiology of Cardiac Muscles: As aptly stated by Clark, human heart is a complex and complicated pump with tremendous reserve power, so much so, that the number of cardiac pulsations in a man of 70 years, might have amounted to 2500 million contractions without a second's rest, at a time.

The properties of cardiac muscle comprise:

Contractility	inotropism.
Excitability	chronotropism.
Conductivity	dromotropism.
Tonicity	tonotropism.
Abnormal excitability	bathmotropism.

The normal contraction consists of a wave of excitation, starting from the S.A. node, passing over the auricles, A.V. nodes and ventricles, (Plate XXVI: Fig. 67).

The wave passes at the rate of 1 meter/second. Section of the bundle produces a complete block between the auricle and the ventricle. The vagus and the sympathetic nerves act as reins and spurs, respectively, for the heart. The uncontrolled heart rate is 110/minute in adults.

The heart muscle obeys the *all or none law*, responding maximally to a stimulus. The wave of excitation is followed by a refractory phase, which in turn, may be absolute or relative. During the refractory phase, the recuperative process sets in, preparing the cardiac muscle for the next wave of excitation. The muscle during this phase, is more or less inexcitable.

The force of contraction of the heart depends on the initial length of the muscle fibre—*Starling's Law*. The greater the initial length, due to distension or otherwise, the greater is the force of contraction. The cardiac muscle which cannot run into oxygen debt, consumes a much greater quantity of O_2 in the above condition. Thus, the efficiency of the coronary circulation is essential, as also the supply of glucose and lactate as fuels.

Approximately, about 20% of the cardiac output from the left ventricle passes through the coronary circulation. If this is hampered, due to vascular or any other disease, the nutrition of the heart is impaired. Cardiac muscle also contracts better against a certain amount of resistance, which is furnished by the aortic pressure, which, in turn, is dependent upon the tone of the peripheral arteries, as also peri-

pheral resistance. The cardiac output depends on the rate and volume of blood pumped out in each contraction.

The amplitude of contraction is controlled by the tone of the cardiac muscle, its rate and the blood pressure. A change in the tonus, due to changes in the rate, high B.P., etc., is destined to affect the efficient contraction and relaxation of the cardiac muscle and the emptying of the chambers.

Nerve Control: The autonomic control is exercised through a complex set up. (Plate XXVI; Fig. 66).

Vagus. It slows down the heart by acting on the auricles and the junctional tissues. The right vagus supplying the S.A. node, slows the right heart more than the left, which latter, supplies the A.V. node. The diastolic phase is increased by vagal action. After continuous vagal stimulation, the heart may break away from the vagal effects. This is called '*vagal escape*'. The normal adult is vagotonic, as opposed to children and the aged, in whom, the vagal tone is less.

Sympathetic. It increases the amplitude and rate of the heart, improves conduction in junctional tissues, increases the irritability of the myocardium and causes coronary dilatation.

Vasomotor centre. It is situated in the medulla and regulates the tone of arterioles by the sympathetic nervous system. V.M. centre sends out continuous slow impulses to the arterioles to maintain their normal degree of tone.

Hypothalamus. Efferent fibres from the hypothalamus control the vasomotor and cardiac centres in the medulla, the posterior nuclei controlling the sympathetic, while the middle nuclei, the parasympathetic activity.

Reflex Regulation: (a) A large number of areas in the wall of the blood vessels have nerves which are sensitive to the changes in pressure. These nerves are connected to the vasomotor centre. Pressure sensitive areas are in the carotid sinus (in the internal carotid artery, near its bifurcation) and aortic arch.

(b) Normal blood pressure causes a certain degree of stimulation of this pressure sensitive nerves which then cause a certain amount of inhibition of the vasomotor centre and stimulation of the cardiac-inhibitory centre. When the equilibrium is reached, blood vessels acquire a particular tone and the heart beats at an appropriate rate. Increase of B.P. stimulates these nerves, causing greater inhibition of the V.M. centre, lowering of vascular tone with resultant fall in B.P. stimulation of the cardio-inhibitory centre and bradycardia. Opposite changes occur when the B.P. falls.

(c) Pressure sensitive nerve endings in the right auricle and in the base of the big veins, have connection with the cardiac centres and whenever an excessive volume of blood collects in the right auricle and big veins, compensatory tachycardia occurs for quickly pumping the blood out of the heart, thereby reducing venous and right auricular pressure. This is known as *Bainbrige-reflex*.

Cardiac Reserve: To fulfil the normal circulatory requirements, the heart does not have to utilise all its forces. The heart has plenty of reserves which are brought into use during physical exertions with increased circulatory demands.

Any decrease in this reserve also decreases the ability of a man to carry out his normal circulatory functions and this state is called *Cardiac failure*, which may occur from many causes, of which, the following are the important ones:

- (a) Increased workload, as in hypertension, aortic stenosis, coarctation and severe anaemia.
- (b) Malnutrition of myocardium in beri-beri or coronary occlusion.
- (c) Myocardial inflammation as in diphtheria.
- (d) Mechanical obstruction from outside, as in 'constrictive pericarditis', preventing cardiac expansion.

To a certain extent, the heart tries to compensate this diminished reserve by the enlargement of its muscle. This enables a man to remain normal at rest. But whenever work is excessive, the diminished ability of the heart makes him breathless. This is known as *compensated heart*. When the reserve falls still more, even the resting man becomes dyspnoeic and this is what is known as *uncompensated heart*.

Coronary Vessels: These are the right and the left, the left dividing into circumflex and the anterior ascending branch, going to the left A.V. groove and the apex and giving septal branches, respectively. The auricles are supplied by these and the right and the left ventricles are supplied by the right coronary. The capillaries lie parallel to and in contact with the muscle fibres. The venous system comprises the (a) sub epicardial network, draining in the right ventricle and (b) a deeper network directly draining into the cavity of the heart.

The factors affecting the coronary blood flow are: (a) mean arterial pressure, (b) resistance in the pulmonary artery and aorta (c) innervation and (d) anoxia. Prolonged use of vasodilators have been found to promote interarterial anastomosis, besides the lifting of coronary

resistance and induction of coronary dilatation in pigs, which are similar to man, in respect of collateral coronary circulation.

General Circulation: In an adult, the volume of the circulating blood is about 6 litres and in a resting adult, the cardiac output is 5 litres per minute, which later, may increase 4-5 folds during heavy exercises. The increase is affected by an increase in the rate of circulation.

The velocity of circulation in the aorta is about 200 mm while that in the capillaries, is only 1 mm/sec. During the active functioning of an organ, the capillary circulation may increase 5 times. In the maintenance of normal circulation, therefore, the capillary tone is of very great importance and in anaphylactic shock, even a single organ like the liver, is sometimes capable of containing 1/4 of the total volume of blood in the body.

The cardiovascular system actually comprises *two sets* of pumps—the right and the left side of the heart and two sets of distensible vessels: the pulmonary and systemic offering resistance to the flow of blood through them. The mean pressure in the pulmonary artery, is only 15-20 mm. Hg., while that in the systemic vessels, is 100 mm. Hg.

Normally, the blood pumped out by the left ventricle, should be the same as that which is received from the right ventricle and so should be the case for the right side of the heart. If it is not, stasis, oedema and collection of fluid in the tissues, occur.

The cardiac output depends on the venous return and *vice versa*. Both these valves are equal normally and express the volume flow of blood per minute through the C.V. system.

Normal Blood Pressure: It depends upon the cardiac output, peripheral resistance and volume of blood and also the elasticity of blood vessels, the tone of which is regulated by the vasoconstrictor and vasodilator fibres, under the control of the 'vasomotor centre', referred earlier.

Distribution of Blood: This is grossly unequal, the vital organ representing 10% of the body weight, get 33% of blood supply and the rest 90% gets only 67%. The vasomotor control, for obvious reasons, is weak in brain, heart, liver and kidneys, because of continuous activity.

Cardiac Arrhythmias: The normal orderly sequence of contraction of the different chambers of the heart occurs from the orderly progression of the excitable wave from the S.A. node to the auricles, A.V. node, right and left bundles of His, Purkinjee's fibres and ventricular myocardium. However, every part of the heart is capable of contrac-

ting rhythmically, if left alone. Thus, the ventricle has a spontaneous rate of 40/min. The rate of auricles is higher, whereas the rate of discharge of impulses of S.A. node is 120-150/min. That is why the auricles, in spite of their low rhythmicity, beat at a faster rate in accordance with the directions of the S.A. node. The fast rate of the S.A. node is kept at check by the vagus. Hence the normal heart rate is 70-80/min.

In the above context, the pathogenesis of a few cardiac conditions affecting the rhythm, is discussed below:

(a) If the conducting tissue, at any part, stops functioning (e.g. due to infection or coronary thrombosis), the parts of the heart beyond this site, may start beating at their slower inherent rates. Thus, if the A.V. node or the bundle of His is blocked completely, though the auricles may beat at the same rate, as the S.A. node, the ventricles assume the idioventricular rhythm of 40/min. and not necessarily follow auricular beats. This condition is called *complete heart block*.

(b) If the A.V. conducting tissues become depressed or if the auricles discharge impulses at a rate faster than what the A.V. conducting tissue can handle, all impulses may not go to the ventricle. It may be possible that for every 4 auricular contractions there may be 2 or 3 ventricular contractions only. This is *partial heart block*.

(c) If a certain part of the ventricle becomes temporarily irritable (due to anoxia, etc), it may discharge an impulse in addition to the normal ones coming from the S.A. node. The extra contraction that results is known as *extrasystole*.

(d) If a certain part of the auricles or ventricles becomes irritable and start discharging impulses at a rate faster than the S.A. node, the rest of the heart starts obeying this focus, instead of the S.A. node. Depending upon the site of the origin of the impulses, the condition may be called *auricular* or *ventricular paroxysmal tachycardia*. The rate may be near about 180/min. or more. The condition is short-lived and may repeat periodically.

(e) If the auricles start beating, as a whole, at a rate of 200-300/min. all the impulses do not travel to the ventricles which responds less rapidly. This condition is called *auricular flutter*.

(f) If certain parts of the myocardium become diseased and more than one point of the irritable foci are set up, a large number of impulses irregularly travel all over the myocardium, resulting in, fast, irregular, ineffective wreathing contractions at the rate of 450/min. or above. If this occurs in the auricle, the ventricles beat at a slower rate, irregularly and the condition is called *auricular fibrillation*. If it occurs in the ventricles, it is called *ventricular fibrillation* and becomes rapidly fatal.

Circus movement: This ingenious theory of Lewis (Plate XXVI; Fig. 68), which was the basis of E.C.G. studies, though not fully upheld now, has aimed at explaining the mechanism of impulse conduction in cardiac muscle, in normal and arrhythmic conditions and also drug actions ameliorating the latter.

According to this, an impulse beginning, say at X, travels towards Y, along both the sides of the circular strip of myocardium. When the two meet at Y, they cannot travel further, because of each wave of excitation, leaving an area of inexcitable tissue in a refractory phase. If due to some circumstances, the impulse from X travels only along one side, it can travel back through the other side too.

By the time, the impulse circles round and comes back to X, the tissue which was inexcitable, becomes excitable again and the impulse can go round again and again, as in D. The head of the wave tries to catch the tail, in vain and thus a circus movement results. In other words, if the conduction of impulses occurs at a rate slower than the duration of the refractory period, the circus movement is favoured. Any drug which can make the refractory period long or the conduction fast or the path of impulse short, will narrow the excitable gap and once the head catches the tail, the impulse cannot progress.

Cardiac Failure: This may be *left* or *right-sided*.

Left-sided failure—It is more particularly due to rheumatic carditis, hypertension and coronary insufficiency. This results in compensatory hypertrophy, followed by, dilatation and left ventricular failure. It is characterised by pulmonary oedema, fall of B.P. and coronary ischaemia.

Right-sided failure—In this condition, the output of the right ventricles is considerably reduced, leading to a rise in the venous pressure, engorgement of capillaries and veins and stasis of blood. It is a *low output* cardiac failure, which is characterised by the enlargement of liver, cyanosis, ascites, oedema of dependent parts and low urinary output.

Methods of Evaluation: With the recently advanced techniques, it is now possible to evaluate the effects of cardio-vascular drugs, both experimentally, as well as, by *clinical trials*, in a much more precise manner than before. The techniques usually followed are:

(a) Study of drug effect on isolated frog and mammalian heart; heart *in situ*, heart-lung preparation, B.P. and auriculo-ventriculogram studies, also papillary muscle technique of Cattell.

(b) Study of coronary flow changes by 'Langendorff's technique' or with the help of electromagnetic flow-metre, thermostromuhr and dye dilution methods.

(c) Study of drug effect by inducing experimental *cardiac failure* by various devices—decreased venous return by the technique of Herschfeld, calcium deficient solutions, phenobarbitone, etc. and thus determining the beneficial effect of drugs, in this condition.

(d) Induction of *auricular fibrillation* by local application of acetylcholine or aconitine, *flutter* by crushing a large strip of auricular muscle and stimulating the auricle electrically, with square-wave impulses, induction of *ventricular arrhythmia* by one or two stage ligation of anterior or descending branch of the left coronary artery or by administration of isoprenaline, benzene, chloroform or local application of adrenaline.

(e) *Clinical evaluation* of cardio-active drugs in congestive heart failure cases by the method of 'Harry Gold and Cattell'.

Prolongation of the refractory period is indicative of antifibrillatory action of drugs. This can be measured by stimulating the isolated rabbit auricle with shocks of increasing frequency, till missing of beats occurs. The drugs which prolong the refractory period, reduce the maximum frequency to which the auricle can respond without missing any beat, possess antifibrillatory action.

Electrocardiography: In many of the above experiments, the cardiac functions are monitored by recording the electrical changes from the contraction of different parts of the heart, in a normal sequence, which is represented electrically by a complex waveform in an E.C.G. in which, P represents the auricular contractions, QRS the ventricular contraction (depolarisation) and T the ventricular repolarisation.

In arrhythmias, P wave is replaced by an ill-defined fibrillatory wave, along with too fast and irregular rates of QRST complex. Heart rate and A.V. conduction are assessed by noting the RR and PR interval, respectively. Widening of the QRS complex is suggestive of delay in the conduction velocity, while depression of T wave and ST segment, indicates myocardial damage, as in myocardial infarction.

All these techniques have greatly facilitated the study of drug action in experimental animals, as well as in cardiac conditions, leading to the discovery of a large number of important drugs, in different cardiac disorders, with increasing efficacy and safety.

CHAPTER

29

DRUGS ACTING ON THE HEART

CARDIAC GLYCOSIDES AND ANTIARRHYTHMIC DRUGS. SCOPE OF ACTION AND USES

[Drugs acting on the heart, comprise (a) Cardio-active digitalis glycosides and (b) Anti-arrhythmic quinidine compounds.

The digitalis group of plants, comprising *digitalis*, *strophanthus* and *squill*, possess important glycosides, of which, digitoxin, digoxin, ouabain and scillaren are the important ones. Their main cardiac actions refer to the myocardium, improving ventricular efficiency with positive inotropic and negative chronotropic actions, increased cardiac output and venous return, thereby improving peripheral circulation and oedema in congestive cardiac failure, for which, digitalis is the drug of choice. Ouabain has a quicker but less sustained action and finds its indication sometimes in emergency cardiac failure, along with I.V. digoxin. Digitalis also has diuretic action in cardiac oedema, which is further, potentiated by mercurial and thiazide diuretics.

The principal antifibrillatory drugs are three—(a) Digitalis (b) Quinidine and (c) Procainamide, which are used in different types of rhythmic disorders of the heart—paroxysmal tachycardia, auricular fibrillation and flutter. Though quinidine, is an overall cardiac depressant, with negative inotropic and chronotropic actions and should be more specific in cardiac arrhythmia, in actual practice, digitalis along with quinidine and prostigmine are actually used in auricular fibrillation, with temporary success, as palliative measure. So far as the ventricular fibrillation is concerned, there is hardly any effective drug offering dependable result. However, *pronestyl* and methods of defibrillation, are made use of, wherever the facilities for the latter, prevail.

The other antifibrillatory drugs belong to many newer groups: *Antihistaminics*—antazoline; *Antimalarial*—mepacrine and chloroquine; *Antispasmodics*; *Local anaesthetics*; potassium, steroids; *Antiepileptics*—dilantin. Their clinical efficacy, however, is not yet fully assuring.]

Drugs acting on the heart comprise two principal groups of pharmacologic agents:

1. Cardio-active glycosides — digitalis, strophanthus and squill.
2. Antifibrillatory drugs — quinidine, digitalis, pronestyl and mepacrin.

There are many other *minor* drugs possessing the above properties

but in view of their nonestablished status in therapeutics, they will not be studied in this chapter.

CARDIOACTIVE GLYCOSIDES

The digitalis group of drugs comprises *three* principal plants — digitalis, strophanthus and squill, all possessing glycosidal active principles.

Digitalis or Foxglove: (Plate XXVII; Fig. 70) grows mostly in Europe. Two important varieties are—(a) *Digitalis purpurea*—official, (b) *Digitalis lanata*, containing the important glycoside — digoxin.

The leaves of the plants are collected on alternate years when flowering, dried in vacuo and packed hermetically, as moisture deteriorates its activity.

Active principles. A series of glycosides, about 1%, present in the leaves, as precursors or native glycosides, which on partial hydrolysis, yield simpler glycosides, as isolated principles. Thus from *Digitalis purpurea*, the isolated glycosides of digitoxin and gitoxin are obtained from the precursor glycosides-*deacetyldigilanid* A and B respectively, which are also obtainable from the precursor glycosides of *digilanid* or *lanatoside* A & B in *Digitalis lanata*. Further, digoxin is obtained from the precursor glycoside-diginalid or lanatoside C from *Digitalis lanata* only.

These glycosides, on acid hydrolysis, decompose into—(a) *aglycone* or *genin molecule*-digitoxigenin and (b) three molecules of *sugar*, *digitoxoses*, $C_6H_{12}O_4$. The pharmacological activity resides in the *aglycone molecule* and the *sugar molecule* helps in the absorption, solubility and persistence of action. These glycosides are either crystalline or amorphous, some soluble in water and others in chloroform. They are bitter and foam on agitation like saponins.

Strophanthus: It grows in Africa and the *seeds* are used for medicinal preparations.

There are *three* varieties of strophanthus—(a) *Strophanthus kombe*, (b) *Strophanthus gratus*, (c) *Strophanthus hispidus*.

Active principles. Strophanthin G or *ouabaine* is obtained from *S. gratus* and strophanthin K obtained from *S. kombe*.

They are colourless, bitter and soluble in water. The *aglycone molecule* is *strophanthidin* and the *sugar molecule* is *cymyrose*.

Squill or Scilla: There are *two* varieties, the *Indian* and the *European*

Plate XXVII

WILLIAM WITHERING AND CARDIO ACTIVE GLYCOSIDES



FIG. 69. *William Withering* (First used digitalis in congestive cardiac failure)



FIG. 70. *Digitalis*



FIG. 71. *Squill*

Plate XXVIII

STRUCTURE AND ACTION OF CARDIO ACTIVE DRUGS

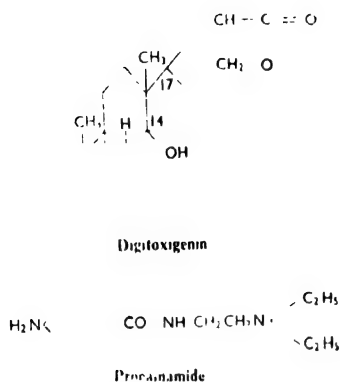


FIG. 72. Structure of some cardio active drugs

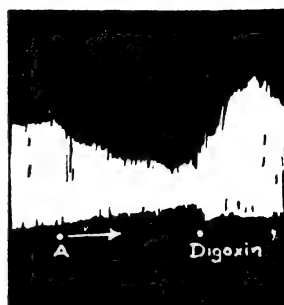


FIG. 73. Isolated rabbit heart: at (A), cardiac failure was induced by perfusion of calcium deficient Ringer Locks solution. Digoxin given at (o) restored the poor contractions to normal.

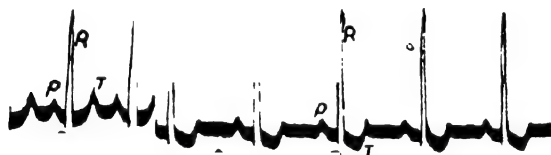


FIG. 74. Toxic effects of digitalis (\uparrow) on ECG. Note the flattening of T waves and depression of ST segment.

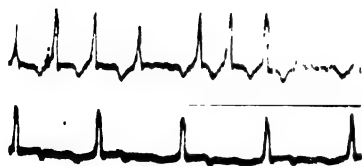


FIG. 75. Electrocardiographic tracings of a patient of auricular fibrillation (upper panel) and its subsequent conversion to normal sinus rhythm (lower panel) after quinidine.

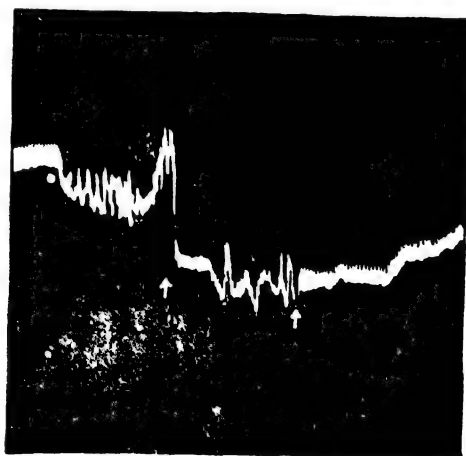


FIG. 76. Effect of digitalis on Cat B.P. by slow I.V. infusion.

or the red and the white. The *corm* or bulb is medicinally used (Plate XXVII; Fig. 71).

Active principles. *Scillaren A* is crystalline and *Scillaren B* is amorphous and toxic.

They are very little soluble in water and decompose in air. The *aglycone molecule* is known as *scillaridin*, while the sugar is known as *rhamnose*.

DIGITALIS

History of Discovery: This was a great landmark in the history of development of pharmacology and therapeutics and occurred in three distinct phases:

From 1542-1776: Discovery of the plant and its minor actions other than cardiac.

From 1776-1900: The memorable work of William Withering (Plate XXVII; Fig. 69) and Ferrier, discovering the cardiac and diuretic properties of the plant.

From 1900-todate: Chemical, pharmacological and clinical studies by a galaxy of workers to name a few—Schmidberg, Cushny, Mackenzie, Nativelle, Stoll and Gold.

Chemistry: This is extremely complex. From the work of Stoll, Chen, and Windaus, the following are established:

- (a) The structure of digitalis glycosides comprises a sterol body as aglycone and a sugar moiety and *digitoxin* may be considered to be the most representative member (Plate XXVIII: Fig. 72).
- (b) The cyclopentanoperhydrophenanthrene nucleus, with a lactone ring at the 17th position, forms the aglycone.
- (c) The complex sugar molecule is attached at position 3 by esterification.
- (d) The unsaturation of the lactone ring in genin, is necessary for the cardiotonic activity. When the double bond is removed, the typical digitoxin action is lost.
- (e) Other cardioactive glycosides—digoxin and ouabain differ from digitoxin only in the number of OH groups at 3 and 14 positions.

Preparations: Though numerous have been the preparations including infusion, tincture, powder and combinations like Guy's pill, in

actual practice, today, only the following preparations may be considered, of which, the purified glycosides only, are routinely used:

Galenicals	Purified principles
Tinct. Digitalis 0.3-1 ml	Digitoxin 0.1 mg. Digoxin: 0.25 mg/tab/os.
Tinct. Strophanthus 0.45-0.3 ml.	Digitoxin: 0.1 mg. Degoxin: 0.5 mg. and
Syrup scilla 2-4 ml.	Ouabain 0.5 mg. Inj/parenterally.

Assay: Being life-saving drugs, all the digitalis preparations are to be carefully assayed by biological techniques, on cat, frog, guinea pig and pigeons, detailed in chapter 6 and also by embryonic heart tissue techniques. The international standard digitalis powder represents one unit of activity in 100 mg. of powder. The therapeutic unit is 1/10th of the cat unit. The assay, which is carried out in terms of the international standard, is a measure of toxicity.

Actions: The main actions of the digitalis group of glycosides pertain to the C.V. system and most of the other actions revolve round this central action.

C-V system. Its actions in congestive heart failure, so masterly described by Clark, are as follows:

- (a) Digitalis regularises, reinforces and slows down the heart.
- (b) It may or may not improve the coronary circulation, but it markedly improves the passive congestion due to inefficient circulation.
- (c) It removes dyspnoea of rest, water-clogging and oedema, thus producing a veritable resurrection of the patient from the threshold of almost an awe-evoking end.

The above simplified, yet amazingly true, representation of digitalis action in C.C.F. cannot however be accepted without proper analysis of digitalis action, in *normal* and *uncompensated heart*, because the action is not the same in both these conditions.

The main pharmacodynamic action of digitalis rests in its *unique ability* to increase the force of *myocardial contractions*, which is the primary seat of action of this drug (Plate XXVIII; Fig. 73). As will be seen hereafter, all the other salutary effects of the drug revolve round this central effect and this is what is known as the *unitary concept* of digitalis action.

Systolic contraction. Digitalis acts directly on the myocardium and increases the force of systolic contraction. This results in: (a) more

complete emptying of the ventricles, (b) improved diastolic filling, and more so, if the rate is slow, (c) adequate handling of the venous return and consequent fall of venous pressure, (d) shortening of systolic and decrease in diastolic size, resulting in more rest, better filling of ventricles and possibility of carrying out the same amount of work with less oxygen consumption, by the heart.

Cardiac rate. This is variable in different species of animals:

In animals. The vagal slowing of the rate is abolished by atropinisation which is not important in isolated hearts. The action is peripheral and is possibly produced by the sensitising of S.A. node and caroticoaortic receptors.

In men. With normal sinus rhythm, there is insufficient and inconsistent effect. In C.C.F. with normal sinus rhythm, there is relief without cardiac slowing and when occurring, it succeeds the clinical relief. In C.C.F. with tachycardia, the rate is decreased. Improvement of the improperly oxygenated ventricles might also be subscribing to the ventricular slowing. The distended auricles and veins being relieved, the 'Bainbridge reflex' is inhibited, resulting in the slowing of the heart.

Conduction system. There is no action on the S.A. node in therapeutic doses but there is slowing in toxic doses. The conduction system is damped down, the P.R. interval is increased and the A.V. conduction is decreased, though this plays a minor role in the slowing of the heart. In toxic diseases, partial or complete heart block occurs. The heart size is decreased and the cardiac output is increased from the improved ventricular efficacy.

Circulation. The venous pressure is decreased to 5 cm. from 20 cm. of H₂O and the circulatory volume is also decreased, though the cause for this is not known. Ordinarily, there is very little change in the B.P. of normal individuals. It may, however, be elevated in high doses. In C.C.F., systolic pressure is restored to normality and pulse pressure is decreased. There is divergent opinion on the effect of digitalis on the coronary circulation. There is no significant change with therapeutic doses and the drug is not contraindicated in angina pectoris.

Diuretic action. This is paradoxical. In normal persons, as well as in patients with oedema of extra cardiac origin, there is hardly any diuretic effect from digitalis, whereas, in C.C.F., the drug produces appreciable diuresis. This occurs mostly from the improvement of general circulation, as well as of kidney function. Nevertheless, the use of mercurial diuretics, along with ammonium chloride or use of thiazides, is often necessary for enhancing digitalis diuresis.

Electrocardiographic effects. In patients under digitalis therapy, the following E.C.G. changes may occur: (Plate XXVIII; Figs. 74, 75).

- (a) PR interval is prolonged from the slowing of conduction.
- (b) T wave is depressed or inverted. This action is utilised by Gold for digitalis assay.
- (c) Partial heart block (2:1 or 3:1) also occurs.

Digitalis and ions. Though calcium enhances digitalis action, it should not be used with digitalis therapy, as it may enhance its toxicity. The toxicity of digitalis on the myocardium is antagonised by potassium.

Enzymatic action. (a) This refers to the greater utilisation of ATP by the contractile mechanism of the heart and also its adequate storage.

(b) In C.C.F. there is deficient supply of ATP which is corrected by digitalis in the following manner:

- (i) Activation of oxygenation, favouring A.T.P. formation.
- (ii) Facilitation of A.D.P.—A.T.P. conversion.
- (iii) Inactivation of ATPase and ATPdeaminase.

(c) Digoxin competes with cholinesterase and spares acetylcholine for the slowing of the heart.

Metabolism: This knowledge has been greatly facilitated by isotopic and embryonic heart tissue studies.

Absorption of digitalis occurs in varying degrees; from the G.I. tract—digitoxin 100%, digoxin 50% and tinct. digitalis 20% only.

Distribution. Though fairly uniform, there is some selective fixation of digitalis in the myocardium and it is difficult to remove even after prolonged perfusion.

Degradation. This occurs to the extent of 90% and principally by liver, at the rate of about 50/ μ g/day. The glycoside first progressively accumulates in the cardiac tissue and thereafter undergoes a uniform rate of degradation.

Excretion. Principally from the kidneys — about 15% in the first 3 days and small quantities persisting even upto 40 days. The cumulative toxicity of the drug is due to its slow degradation and excretion.

Toxicity: Often unavoidable, as for complete digitalisation almost toxic dose level is to be attained. This is important because in 'digitalis therapy' the 'safety margin' is relatively narrow, the therapeutic dose being half of the toxic dose, which in turn is half of the lethal dose.

The main toxic features refer mostly to (a) *digestive* and (b) *cardiovascular systems*.

Digestive. Nausea and vomiting, due to the stimulation of the chemoreceptor trigger zone and headache, which are the first warning signals, usually. Passive congestion of the stomach in congestive cardiac failure may also subscribe to the vomiting, partially. If it persists, the therapy may have to be temporarily suspended. The above effects may also occur after intravenous digitalis therapy.

Cardiac. (a) slowing of pulse which may even go below 70/min. This may be an important guide for adjusting the dose of digitalis.

(b) coupled or bigeminous beats, due to the alternating extrasystole. This is a much more serious sign of toxic *symptoms*.

(c) ECG changes characterised by depression, followed by inversion of the T wave, and finally

(d) precordial pain and various types of arrhythmia, including cardiac arrest and ventricular fibrillation.

STROPHANTHUS

This is another important cardioactive drug, second in order, though much inferior to digitalis. Its actions, though essentially similar to it, differ in certain respects.

Metabolism: The drug is more irregularly absorbed and hydrolysed in the intestine. Its actions are therefore unpredictable after oral administration. It is a greater irritant for the G.I. tract and may cause diarrhoea, in certain cases.

Actions: Ouabain or crystalline strophanthin G is twice as active as its congener amorphous strophanthin K. After I.V. injection, which is the only effective route of administration for this drug, its actions start in 5 minutes and are maximum in 1 hour. It directly stimulates the myocardium where it is more loosely fixed than digitalis. It is rapidly excreted through urine, about 75% in 24 hours and completely in 5 days after a single dose therapy. Though it effectively increases cardiac output, like digitalis, it does not reduce venous pressure, nor induce peripheral vaso-constriction to the same extent. It is however believed to be capable of inducing diuresis even in normal individuals.

Uses: Not as frequently as digitalis, the special indications being:

(a) **Emergency cardiac failure:** 0.5 mg. I.V., followed by 1 or 2 more

injections, at half hourly intervals, not exceeding a total of 1 mg ordinarily. This is then followed by digitalis therapy, which, while having a longer latent period, produces a more sustained effect on the heart and is also more strongly fixed and slowly excreted.

(b) Hypertensive cardiac patients.

(c) Digitalis intolerant cases.

Caution: Ouabain injection fluid has a concentration of 0.25 mg/ml. and being an irritant, care should be taken in not puncturing the vein and cause any extravasation at the site of the injection.

SQUILL

This also resembles digitalis and has a fairly powerful cardiotonic action in the isolated mammalian heart. It has an irregular absorption and is an irritant and reflex expectorant. Its cardiac action is quicker than digitalis but much slower than strophanthin. It is not only not a drug of emergency but very rarely used also. It is a reputed diuretic and expectorant but causes marked G.I. irritation and diarrhoea.

Squill used to be used in patients with cardiorespiratory and renal involvements, particularly in digitalis intolerant cases, but with no special advantages.

Its use in right sided cardiac failure with oedema and pulmonary complications and also in the form of Guy's pill; containing digitalis, squill and mercury, has been discarded and because of its insignificant efficacy but marked toxicity, it has been deleted from the Pharmacopoeia.

Actions Compared: All the three drugs while possessing the common characteristics of cardiotonic, diuretic, vasoconstrictive and gastrointestinal irritant actions, differ from one another in certain respects, leading to varying degrees of clinical applications, in cardiac failure cases.

(a) Digitalis and squill possess limited solubility and have the advantage of oral use, while strophanthus glycoside is markedly soluble and meant mostly for I.V. use.

(b) Of the three drugs, only digitalis has a slow but durable fixation on the myocardium (not even washable easily), slow and prolonged action and excretion, leading to the much desired cumulative action in C.C.F. for which it is the drug of choice.

(c) From the comparative study of onset, peak blood level and dura-

tion of action of major cardiac glycosides, as represented in the underlying table, it is evident that from the standpoint of the relative rapidity of action, the order is ouabain-deslanoside-digoxin and-digitoxin, which last is the slowest.

	Digoxin	Digitoxin	Deslanoside	Ouabain
Onset	5-30 min.	25-120 min.	10-30 min.	3-10 min.
Peak	1½-5 hrs.	4-12 hrs.	1-2 hrs.	½-2 hrs.
Duration	2-6 days	14-21 days	3-6 days	1-3 days

(d) The overall activity and use of digitalis in cardiac failure, from most of the causes, are the maximum and outweigh the other two. After the discovery of digoxin, the special advantages of ouabain in respect of its rapidity of action, though partly neutralised, it may still be sometimes used in emergency cardiac failure cases, where extreme speed, as detailed in the table above, is needed, followed by 2-3 injections, by oral digoxin. Squill or Scillaren could now be almost forgotten and deleted from cardiac therapeutics, without any inconvenience to the patient.

SCOPE OF DIGITALIS THERAPY

This is precise, specific and without any ambiguity, based on—(i) Scientific knowledge of digitalis action. (ii) Correct diagnosis and indication and (iii) Close supervision of patient in view of prolonged therapy, almost at toxic level — a potent drug therapy capable of doing good, as well as harm, when wrongly used. Further, the major indications of the therapy are a few only, while the minor traditional uses still persisting, are many, implicating all the same the risks of toxicity hazards.

Congestive Cardiac Failure: This is by far the most important use of digitalis, irrespective of whether the failure is predominantly of the left or of the right side or of both. The failure may be accompanied by fibrillation, cyanosis, pulse deficit, oliguria and oedema. Arrhythmia may modify the response but not alter the indication. It is particularly useful in failures resulting from the overload of hypertension, valvular lesions or arterio-sclerotic heart diseases. It does not produce the best results in cases of thyrotoxicosis, hypoxia or thiamine deficiency types of cardiac failures. Similarly, it is not of much benefit in cases of myocardial poisoning from cardio-toxic drugs or diphtheria.

With appropriate digitalis therapy, dyspnoea—both exertional and nocturnal, cough, cyanosis, chronic congestion of viscera, oedema and oliguria, all regress and a veritable resurrection of the patient returning to normality again, occurs and the patient is almost completely transformed by 2-3 weeks of treatment. The diastolic size of the heart and venous pressure are decreased, while cardiac output, circulatory velocity and diastolic phase of the cardiac cycle, are enhanced. The vital capacity and alveolar CO_2 content, are increased and the arterio-venous O_2 difference is reduced. If tachycardia is present as a compensatory mechanism of the failure, the same is set right by digitalis, thus improving functional efficiencies of the ventricle.

After digitalis therapy, when the failing heart returns to the state of compensation, its use in the form of a maintenance dose, has still to be continued as a preventive measure against future recurrence. Similarly, it is now believed that in potential heart failure cases in elderly persons with enlarged heart of hypertension, it may be used with some benefit as a prophylactic measure, before clinical manifestation of heart failure occurs.

Its action in non-fibrillating heart is less dramatic and in post-infarction shock conditions, doubtful.

Auricular fibrillation: Even in the absence of C.C.F., digitalis is often indicated in fibrillation for slowing down the rate, improve ventricular efficiency and prevent cardiac failure. The slowing is produced by its inherent action on the conduction system and not on the S.A. node and thus it acts not as a curative but as a palliative. If the fibrillation is associated with other conditions like thyrotoxicosis, that underlying condition, should also be simultaneously treated.

Auricular flutter: Digitalis is used in this condition even in the absence of any congestive failure. It may produce any of the following desirable effects—(a) Restoration of the normal sinus rhythm in certain percentage of cases. (b) Flutter changed to fibrillation which is in more unstable condition and on withdrawal of the drug, the normal rhythm is established in about 30% of cases. (c) The degree of A.V. block is increased e.g. 4:1 is changed 2:1 by increased vagal or reduced adrenergic tone. The A.V. nodal conductivity is increased and any sudden doubling of the ventricular rate sets the condition right.

Paroxysmal tachycardia: Arterial and A.V. nodal types, are the most frequent ones. Digitalis is helpful and acts by reflex vagal stimulation from its I.V. use. Cases requiring prolonged prophylaxis, need

quinidine. Care should be taken to eliminate paroxysmal supraventricular tachycardia with partial A.V. block, induced by digitalis intoxication, before prescribing this drug in such cases.

Other conditions. The drug is *ineffective* in—(a) Ventricular tachycardia in which antifibrillatory drugs and not digitalis, should be used. Potassium is beneficial if this has occurred from digitalis. (b) Tight mitral stenosis with pulmonary congestion and normal rhythm. (c) Constrictive pericarditis. (d) Angina pectoris. (e) Myocardial infarction. (f) High output cardiac failure, as in anaemia. Further, there is no rational basis for its erstwhile use in: (a) Myocardial degeneration. (b) Pneumonia. (c) Postpartum haemorrhage along with ergot and quinine. (d) General diuretic and (e) General tonic for heart. It is definitely contraindicated in (a) Extrasystole and (b) Heart block, as in Stokes-Adam's syndrome.

Methods of Digitalisation: These are of importance, inasmuch as they have bearings on the knowledge of drug actions and disease processes.

Till recently, *Tincture Digitalis* with a potency equivalent to 100 mg of powder or 0.1 mg. of the *active glycoside*, representing 1 unit of activity, has been in use, following—(a) *Slow or classical* or (b) *Rapid digitalisation methods*, the *initial dose* being worked out from the Eggleston's formula as 15-20 ml. of a standard tincture, spread over 4-5 days in the former, or in 3 doses of 6, 4 and 2 ml. at 6 hourly interval, in the latter, followed by a *maintenance dose*, calculated as 1/15 of the initial *loading dose*, from its rate of breakdown in the body, i.e. 1-2 ml./day, taking the *apex beat* of 70-80 as guide of full digitalisation and not allowing it to go lower, for risk of toxicity. The tincture being relatively unstable, its use has now been restricted and/or replaced by the isolated glycosidal principles.

In the cases of *Digoxin*, which has a satisfactory *oral absorption*, full digitalisation can be effected by the oral administration of 1.5, 1.0, 0.5 and- 0.5 mg. at 6 hourly interval in 24 hours if there is no urgency, as is usually the case; alternatively by giving 0.5 mg t.d.s. on the first day — 0.25 mg. t.d.s., the next day and 0.25 mg. t.d.s. thereafter, until heart rate is controlled, signs of failure relieved or mild toxic symptoms ensured. The *maintenance dose* in digitalis therapy is the maximum dose tolerated by the patient and is more than 1/15 of the total quantity, present in the body, at any particular time. In cases of *extreme urgency* or *persistent vomiting*, *digoxin* or *ouabain* 0.5 mg. I.V. repeated after 6 hours and thereafter routine oral therapy, should be prescribed.

Diuretic adjuvants: These are often needed to relieve the water load and oedema in patients. After the discovery of organic *mercurials*, the older diuretics had lost their place and these were used in conjunction with an acidifying *ammonium chloride*, for draining the oedema fluid, not managed by digitalis alone. After the discovery of *diamox* and *thiazides*, these have, in turn, replaced the mercurials. The latter have the advantage of oral administration, less toxicity and better efficacy.

Chlorthiazide. 1 gm/day and *trihydrochlorthiazide* or *hydroflumethiazide*—0.1 g per day, are used as tablets or capsules—4 days/week, with potassium chloride 0.2 gm. on days when the former is not given. Action starts in 2 hours and is completed in 12 hours. They are much less toxic than mercurials and are particularly indicated in left-sided failure. In resistant case to mercurials, *aminophylline*, may be tried. *Chlorthalidone*—is a new potent compound, active in much smaller doses of 100-200 mg/os/once or twice/week. It constitutes an important adjuvant in hypertension also. It resembles chlorthiazides with regard to its effects on sodium and potassium excretion and is a good adjuvant in hypertension cases. *Spironolactone*—the aldosterone-inhibitor, is of value as diuretic, in the treatment of cirrhotic, rather than cardiac oedemas. It is indicated in refractory cardiac oedema cases, in combination with chlorthiazides. The above therapy does not preclude the necessity of salt, fluid and dietetic restrictions and also paracentesis, venesection and O₂ therapy, in the management of cardiac failure.

Rationale of Therapy: From the foregoing, it is apparent that adequate knowledge, with regard to cardiac disorders, in general, and C.C.F. in particular, have now been acquired, enabling us in understanding their pathogenesis, fairly clearly. The same remark applies also to our knowledge of drug action in these disorders, with special reference to digitalis in CCF. The chemistry, physiology, action and toxicity, are fully established, including the bio-chemical and cellular mechanisms of these actions, their fixation and excretion. All these together constitute the scientific basis of digitalis action in CCF and other cardiac conditions, which is unassailable by any other drug, hitherto known.

ANTIARRHYTHMIC DRUGS

These constitute a group of drugs which correct the abnormal rhythm of the heart and are known as *antifibrillatory* or *defibrillatory* agents. They are in fact, myocardial depressants, in the majority of cases.

Physiological Considerations: The heart starts its rhythmic contractions in the intra uterine life and continues the same till death. This may be affected or disturbed by a number of physio-pathological conditions producing what is known as *cardiac arrhythmias* of varying types: (a) Extra systole, (b) Auricular or ventricular paroxysmal tachycardia, (c) Auricular flutter, (d) Auricular and ventricular fibrillation, (e) Complete or partial heart block.

Some of these conditions may be of a physiological type without any organic change, while in others, permanent damages to the myocardial functioning with disturbances in the polarisation and depolarisation mechanisms of the myocardial cell membrane, may supervene. Unlike in skeletal muscles, the myocardium remains completely inexcitable till the muscle is repolarised for responding to a stimulus and this is welcome, as otherwise, any phenomenon with summation of effect, resembling tetanisation, would have been disastrous for the heart. The modern theory of excitability of the cell membrane also envisages the role of potassium in the causation of cardiac arrhythmias, by affecting both the depolarisation and repolarisation mechanisms. Anoxia, which is one of the predisposing factors, causes efflux of potassium ions.

Classifications: The principal drugs in actual use are only three—digitalis, quinidine and procainamide. Others possessing this activity, but little used in therapy belong to diverse groups, as given below:

Antimalarials.	Mepacrine, Chloroquin and paludrine.
Antihistaminics.	Antazoline.
Local Anaesthetics.	Procaine and lidocaine.
Antispasmodics.	Papaverine.
Adrenergic beta-receptor blockades.	Propranolol.
Cations.	K, Mg and Ba.
Miscellaneous.	Certain barbiturates, reserpine, corticoids, antithyroid and antiepileptic-dilantin.

Sympathomimetic drugs like isoprenaline, methoxamine and mephenteramine are chiefly of value in slow arrhythmias like incomplete heart block, where they act by increasing the heart rate. Unlike digitalis, these cardiac depressant drugs are not only not uniformly efficacious but their actions and uses are also shadowed by their potential toxicities. Further, though the arrest of auricular fibrillation is possible and can be achieved with some of these drugs, no drug is available at present, which can consistently defibrillate the ventricles.

QUINIDINE

It is an alkaloid, obtained from the Cinchona bark, which also yields quinine. It is available as a synthetic compound. The sulphate salt is white, crystalline, bitter. *Solubility*: 1%. *Dose*: 0.2–0.3 mg/4-5 times/day.

Chemistry: It is a quinoline compound and a dextro-isomer of quinine. Its unique antifibrillatory activity had prompted much chemical work from the standpoint of structure-activity-relationship which is still far from established.

In the structure of quinidine, the quinuclidine ring seems to be vital but other simpler structures like triethyl-aminoethanol also possess similar activities. The presence of the tertiary amines, as in procainamide, may also be of value but the quaternary compounds also have this activity. The methoxy and vinyl groups, as well as their alcoholic linkage, have been considered essential but other compounds like cinchonine have disproved this hypothesis. The actual position is that much more knowledge has to be acquired before the riddle could be even partly solved.

Metabolism: It is readily absorbed from the G.I. tract, producing a peak concentration, in blood in 2-3 hours but of short duration. About 75% of the drug is destroyed in the tissues and 25% excreted unchanged in urine.

Actions: In common with its 1-rotatory isomer, it has most of the general actions of quinine—viz. protoplasmic toxicity, antimalarial action, etc. Further, quinidine is endowed with its characteristic actions on the heart, making it suitable for rhythmic disorders of a fibrillatory nature.

Heart. a myocardial depressant affecting excitability, conductivity, velocity and contractility. This direct action is complicated by indirect anticholinergic action of quinidine.

(a) *Excitability*. The threshold for electrical stimuli is increased by 10-25%, at a concentration of 6 mg/litre, in isolated preparations of rabbit atria. This may account for the depression or abolition of the ectopic impulse generation.

(b) *Refractory period*. This is increased by 50% in rabbit atria at the same concentration. This is observed in intact dogs also. The duration

of action-potential, recorded by microelectrode methods, does not necessarily accompany the effective refractory period. This means that the tissue remains refractory for an appreciable interval after the full restoration of resting membrane potential.

(c) *Conduction velocity.* The conduction velocity, in isolated atria, purkinjee fibres and ventricular muscles, is increased. The reduced excitability and decreased state of repolarisation lead to the depression of conduction. Quinidine might be reducing the availability of sodium carrier, which may delay repolarisation and diminish the excitability.

(d) *Pace-maker activity.* In therapeutic concentrations, the action potentials of the cells of the S.A. node are increased. Ectopic pace maker activity is inhibited and it is this latter which is therapeutically useful.

(e) *Vagal blocking.* Quinidine presents cardiac slowing produced by direct or reflex vagal stimulation and by cholinergic action. Thus, in spite of the depressant action on the pace maker, the heart rate is increased in anaesthetised animals and also in man. The cardiac acceleration is partly due to the anticholinergic action but the reflex increase of adrenergic influences cannot be ruled out. This partially accounts for the abolition of auricular fibrillation induced by digitalis in experimental animals. Atropine also produces similar actions. The anticholinergic action on the A.V. node is important, as cholinergic influence increases A.V. conduction time and refractory period. This may sometimes prove to be the hazard and parasympathomimetic drugs, in that case, fail to terminate paroxysmal supra-ventricular tachycardia, in patients receiving quinidine. None of these effects of quinidine on the ventricle however is affected by the vagal blockade.

(f) *E.C.G. changes.* Sinus tachycardia results from its anticholinergic action and with higher doses, S.A. block results from the depression of conduction, as well as of excitability. The Q.T. interval is prolonged and so also the Q.R.S. complex, which latter, is a danger signal in the clinical use of the drug. Quinidine may also cause unpredictable abnormalities of rhythm, in the digitalised hearts.

(g) *B.P.* There is a fall of B.P. from peripheral vasodilatation, particularly after parenteral uses of comparatively higher doses.

Actions Analysed: The actions of quinidine and the underlying mechanisms involved in the improvement of fibrillation, are not only complex but several factors join together to subscribe to this effect. The excitatory gap being diminished, the circus movement is stopped and as Osler used to say, 'the head of the wave, catching the tail'. Further, the increasing number of aberrant waves getting suppressed, the atrium

becomes more quiescent, permitting the S.A. node to take up the charge. During the process of working, the atrial flutter sometimes sets in and because of the reduced A.V. block, paradoxical ventricular tachycardia might occur, causing harmful effects. During this episode, the slowing of conduction and prolongation of refractory period may sometimes act antagonistically. If the former effect is predominant, cure occurs and if the latter action dominates, the failure of the treatment results. The exact mechanisms of these actions have not yet been established but it has been suggested that the inhibition of the lactic dehydrogenase enzymes preventing the breakdown of sugars in the cardiac muscles, thus altering its function, and also the competitive blocking of acetylcholine for use by the cardiac muscles, might be responsible for the antifibrillatory actions of quinidine.

Toxicity: A potentially dangerous drug which has caused many deaths due to injudicious use. Toxic manifestations comprise the following:

(a) *Idiosyncrasy*—which is much stressed but all the same, quite rare. Urticaria and drug fever may occur as allergic manifestations. (b) *Cinchonism*—with tinnitus, blurring of vision, vertigo, tremor and sometimes diarrhoea. These stop after the suspension of therapy. (c) *Embolism*—from dislodgement of clot from the atrium after it starts beating effectively. (d) *Cardiovascular and haemopoietic systems*—may be the main targets, causing thrombocytopenia, purpura, vascular collapse, shock and myocardial depression. These can be treated by norepinephrine, angiotensin and molar sodium lactate solution. The reversion of quinidine toxicity is however, demonstrated by the reappearance of positive inotropic action of the heart.

Quinidine and Digitalis Compared: The cardiac actions of digitalis and quinidine make both of them suitable for the treatment of *auricular fibrillation* and yet their actions are of different types. Their relative roles in the treatment of arrhythmia has been lucidly explained as:

(a) Quinidine cures fibrillation by restoring the normal sinus rhythm. (b) Digitalis improves fibrillation by making ventricular rate slower, more regular and more forceful, by acting on myocardium and conduction tissues. But unlike quinidine, digitalis does not lengthen the refractory period of the auricle sufficiently to interrupt the circus movement. (c) The restoration of ventricular efficiency and not cure of fibrillation is aimed at when digitalis is used, whereas the restoration of the normal sinus rhythm is the objective when quinidine therapy is given.

COMPARATIVE TABLE**Cardiac actions**

<i>Drugs.</i>	<i>Contractility inotropic effect.</i>	<i>Excitability chronotropic action.</i>	<i>Conductibility dromotropic action.</i>	<i>Ectopic pace-maker bothmotropic action.</i>	<i>Refractory period.</i>	<i>Vagal effect.</i>	<i>Potassium efflux</i>	<i>Response to adrenaline and nor-adrenaline.</i>
Digitalis action.	increased and more so, in stretched heart.	depression.	slowing; more of A.V. nodal area.	rate slowed by direct and also vagal effect.	shortening, excepting A.V. nodal area.	increased.	increased.	increased
Quinidine action.	nil or a depression of damaged myocardium.	depression.	slowing	slowing more in high doses even arresting of pace maker.	lengthening of all areas.	antiacetyl choline effect.	decreased.	decreased.
E.C.G. changes								
NORMAL HEART				ARRHYTHMIC HEART				
	<i>P-R Interval</i>	<i>Q.R.S. Interval</i>	<i>Q.T. Interval</i>	<i>S.T. Segment</i>	<i>Atrial fibrillation.</i>	<i>Auricular flutter rate.</i>	<i>Premature ventricle systole.</i>	
Digitalis	lengthened.	widened.	shortened	depressed.	shortened.	increased.	increased.	
Quinidine	lengthened.	widened.	lengthened.	no change	lengthened.	decreased	decreased or eliminated.	

The above simplified and yet amazingly clear and expressive comparison of the two essential antifibrillatory drugs, by Cushny, can now, in the light of detailed experimental studies, since carried out, be supplemented by observations, vide Table supra, page 392.

Uses. These are several and refer to the disturbances of rhythm of the atria or of the ventricle. The important conditions are: (a) Auricular fibrillation, (b) Auricular flutter, (c) Premature systole, (d) Ventricular tachycardia, (e) Paroxysmal supraventricular tachycardia and (f) Arrhythmia following myocardial infarction, (g) Other conditions such as (i) Wolfe-Parkinson-White syndrome (ii) Angina pectoris, (iii) Hyperactive carotid sinus reflexes, (iv) Fibrillation following cyclopropane anaesthesia and cardiac surgery and (v) Hiccup.

Contraindications (i) Quinidine sensitive patients, (ii) Severe cardiac failure or marked myocardial damage from coronary infarction with failure (iii) Bacterial endocarditis (iv) Chronic fibrillation and valvular disease. (v) Aged individuals (vi) Hyperthyroidism, (vi) Ventricular tachycardia after digitalis.

The above are the contraindications and one has to balance the risk due to the disease and the drug and then to choose. Thus longstanding ventricular tachycardia may be treated with quinidine despite the dangers.

As absolute contraindications, the drug should not be used in (a) acute infections (b) heart severely damaged or in acute failure (c) when there is risk of hypersensitivity reactions (d) when the return to sinus rhythm is unlikely or undesirable as in angina pectoris.

PROCAINAMIDE OR PRONESTYL

It is formed by the removal of one atom of oxygen from procaine with substitution by amine. The salt is soluble in water. (Plate XXVIII; Fig. 72b).

Metabolism: The drug is completely absorbed from the G.I. tract and the peak blood concentration is attained in one hour. It is excreted in unchanged form partly free and partly conjugated.

Actions: They are essentially quinidine-like but prompt-depression of excitability, prolongation of refractory period, suppression of rhythmicity and impairment of conduction, contractility remaining unaffected. Unlike quinidine, it does not reduce the cardiac output,

It produces hypotension after I.V. inj. and also possesses anaesthetic effects.

Toxicity: (a) hypotension, (b) leucopaenia and even agranulocytosis, (c) allergic symptoms-rash, asthma, angioneurotic oedema. *Dose:* Oral-1 gm., followed by 0.5-1 gm/4-6 hourly. I.V.-0.5-1 gm, well diluted and slowly injected, at the rate of 25-50 mg/min.

Uses: (a) Ventricular and auricular tachycardia following myocardial infarction or during anaesthesia. It is both preventive and curative.

(b) Recent auricular fibrillation.

(c) Quinidine refractory cases.

(d) In ventricular tachycardia and fibrillation, digitalis is dangerous and should not be prescribed. Quinidine however may be given and if it fails, procainamide—1 gm. followed by 0.5 gm/4 hourly, per os or I.V., may be effective. The injection should be given very slowly.

OTHER DRUGS

Besides the above, a large number of other drugs have also evinced various degrees of antifibrillatory actions. They are not comparable to quinidine or procainamide but as they are not effective in all cases, these newer drugs are also sometimes used, when they fail.

Antimalarials: Many of the synthetic antimalarials have been tried experimentally. Clinically, mepacrine and chloroquine have been used. *Mepacrine* is administered in a dose of 0.3-0.6 gm. The actions are similar to those of quinidine and the drug is useful in cases of auricular fibrillation of recent origin. Its status in the treatment of arrhythmias, is not fully established.

Antihistaminics: Several antihistaminics have been used. Antazoline, diphenhydramine, tripeleminamine are the only ones which have been used clinically and their actions found comparable to quinidine, to a certain measure.

Antispasmodics: Atropine, banthine and amotriphene belong to this group. Atropine at times, is used for correcting atrioventricular conduction, in cases of 'Wolfe-Parkinson-White Syndrome'. Amotriphene is a synthetic congener possessing antiarrhythmic and coronary vasodilating effects. Papaverine also may sometimes be considered for use in these conditions,

Local Anaesthetics: Procaine and Lidocaine have been tried but their serious depressant actions on the myocardium have restricted their use.

Sympathomimetic Amines: Epinephrine and Isoproterenol initiate the activity of the pace-maker. Methoxamine, another pressor agent, also possesses antiarrhythmic activity.

Cations and Anions—Because of the peculiar sensitivity of the heart to ionic environments, potassium, magnesium and barium have been used as antiarrhythmic drugs. *Potassium chloride* depresses both the conductivity, as well as the excitability of the myocardium and potentiates the action of quinidine. It removes extrasystole and may be tried in paroxysmal tachycardia when other measures fail. *Dose:* 1 gm./4 hrly/50s. *Magnesium sulphate* in a dose of 20 c.c. of 20% sol. I.V.—depresses the C.N.S. and also the myocardium and checks auricular tachycardia. Similarly, *Barium chloride* facilitates cardiac conduction and is sometimes tried in 'Stokes Adams Syndrome', with doubtful results. Injected with adrenaline, intra-auricularly, it may resuscitate a heart by increasing its myocardial excitability.

Ambonestyl: An isonicotinamide derivative, it is very effective in preventing and abolishing ventricular tachycardia and hypothermic ventricular fibrillation. It does not depress the contractility nor the conductivity.

Mecholyl and Prostigmine: Their uses in paroxysmal tachycardia has been discussed elsewhere.

1-fegarine, barbiturates, steroids, reserpine, hydroxyzine, adrenolytic and antithyroid drugs and dilantin, have also been tried with undependable results.

The above is an outline of the antiarrhythmic drugs in use at present. Many of them have their limitations and intrinsic defects and the conditions for which they are used, are also very complex. A lot of work with increasingly newer types of synthetic compounds with the use of a large number of ingenious experimental techniques, referred earlier, is going on and it is likely that better drugs than what are available now, would be found in the future, for solving the present difficulties.

THERAPEUTIC CONSIDERATIONS

Rhythmic disorders of the heart cover a wide field, some of which are ordinarily trivial requiring hardly any treatment, while others are

extremely dangerous and not amenable to any effective therapeutic measures and only symptomatic relief is all that can be given. While irregularities in the cardiac contractions are constant features in many cases, the rate may be accelerated or diminished and unevenly spaced, depending on the type of involvement of the A.V. nodes and the conduction system.

Sinus bradycardia. This may be due to the predominance of vagal tone in athletes or tachycardia associated with fever, shock, thyrotoxicosis or sinus arrhythmia, needing very little treatment.

Extra systoles. They arise from some abnormal focus in the heart, leading to premature beats, the site of the focus being in the atria, ventricles and occasionally in the A.V. node. The underlying causes are many—coffee, tobacco, alcohol or organic lesions. The condition is usually managed by dilantin, meprobamate and sedocardil for a few days and in troublesome cases, quinidine, potassium chloride or procainamide, are to be prescribed but no digitalis, which being a causative agent, is contraindicated.

Atrial fibrillation. This condition with rapid fibrillary waves replacing normal auricular impulses, to which the ventricles also respond erratically, may be due to rheumatic or ischaemic heart disease, hypertension and hyperthyroidism. The management comprises (a) Bed rest in hospital and sedatives for 2-3 days. (b) Digitalis for reducing the rate of heart to about 90/min. This prevents the risk of causing ventricular tachycardia. (c) Digitalis is then to be stopped for a day or two, followed by quinidine, in an initial *test dose* of 0.1 gm., followed by 0.2-0.3 gm. 4-5 times a day, for about a week. No drug is to be given in the night. Quinidine should be stopped at the first evidence of toxicity—tachycardia over 140/min. obstinate flutter and ventricular extrasystole. (d) If sinus rhythm is not established in 3 days, the dose of quinidine should be increased. When normal rhythm is established, a smaller maintenance dose of 0.2 gm. t.d.s. may be given for a fortnight, followed by a still reduced dose for sometime (e) There should be a minimum interval of 2 weeks between any two courses.

Atrial flutter. This is a characteristic condition with practically the same aetiological factors as above, with an atrial rate of 250-300/min. to which the ventricle responds at different but regular rates 2:1, 3:1. The patient has a constant tachycardia of about 160 per minute, uninfluenced by position and a characteristic sawline E.C.G. flutter wave. Drug therapy comprises the use of digitalis and quinidine, discussed above.

Paroxysmal tachycardia. This may be (a) supraventricular, atrial or nodal or (b) ventricular. The former is often without any detectable

cause and the latter occurs in patients with ischaemic heart and is consequently serious. Ordinary attacks are often benefited by various types of managements and drug therapy comprises the use of (a) digoxin—1 mg. I.V. or per os., followed by 0.25 mg/4 hourly. If it fails, neostigmine 1-2 mg. I.V. or acetylcholine—10-25 mg. S.C., should be tried. In cases of any undesirable side-effects, atropine 1 mg. should be given. Quinidine 0.4 mg/os/2 h upto 8 doses, may also be tried. For ventricular tachycardia, digitalis is dangerous. Quinidine may be given as above and/or procainamide—1 gm. 0.5 gm/4 hourly I.V.

Heart block. This may either be a S.A. block, due to increased vagal tone and not of great significance or an A.V. Block, in which the conduction between the atrium and the ventricle is impaired. Depression of conductivity is commonly due to some ischaemia or inflammation of the bundle of His. The permanent block is due to coronary disease, aortic stenosis, acute rheumatic fever, syphilis, digitalis therapy, diphtheria and congenital heart disease. It may be latent, partial or complete. Treatment should be directed against the underlying causes and digitalis should never be given, unless the cardiac failure is present. If partial heart block is due to digitalis intoxication, the drug should be stopped and potassium chloride given. Streptococcal infection should be treated by antibiotics, rheumatic condition by salicylates and cortisone and reflex vagal stimulation, by atropine.

Stokes-Adams syndrome. This is a complication in complete heart block, affecting cerebral blood flow and producing syncope and sometimes even convulsions. The position of drug therapy is unsatisfactory and to the most, palliative. (a) Adrenaline hydrochloride 0.3-0.6 ml. I.M. or I.V. or alternatively, methedrine—30 mg. or isoprenaline in usual doses. (b) Use of artificial pace-maker, digitalis, quinidine and ephedrine are often contraindicated in cases with ventricular tachycardia but as a preventive measure, ephedrine 60-120 mg. t.d.s. or isoprenaline—20 mg. t.d.s. sublingually, may be given. Cortisone also may be used because it can reduce the oedema of the bundle of His. Sometimes barium chloride may also be tried.

CHAPTER

30

PHARMACOLOGY OF BLOOD VESSELS

VASOCONSTRICTORS. VASO AND CORONARY DILATORS. ANTIHYPERTENSIVE AND ANTIATHEROSCLEROTIC AGENTS. THEIR SCOPE OF ACTION AND STATUS

[Drugs acting on blood vessels, comprise different groups—(a) Vasoconstrictors, (b) Vaso and coronary dilators (c) Antiatherosclerotic and (d) Anti-hypertensive agents.

Vasoconstriction is ascribed to many pharmacologic agents which may act—(a) On the V. M. centre—analeptics (b) Sympathetic ganglia—nicotine (c) Adrenergic receptors—Sympathomimetic amines and (d) Directly on smooth muscles of vessels—vasoxyl and posterior pituitary extract. They are used principally in hypotensive states: anaphylactic, peripheral vascular and cardiogenic shocks and also as (e) Haemostatic and decongesting agents.

Vaso- and Coronary dilation, though producible both by central and sympathetic depression, as well as by cholinergic stimulation, the most important group is that of the *nitrites*—organic and inorganic; long, medium and short acting, along with papaverine, aminophylline, khellin and nicotinic acid. They find their uses in—(a) coronary disease (b) hypertension and (c) peripheral vascular disorders.

The main action of *nitrites* is only one—a direct musculotropic, antispasmodic action on all the plain muscles, their tone being reduced but not their ability for maximum contraction. Of the large number of old and new nitrites, amyl and octyl nitrites are given by inhalation and have the quickest but shortest duration of action: Nitroglycerine and sodium nitrite have intermediate action and the first, the advantages of sublingual administration also. Erythrityl and pentacrythrityl tetranitrates, mannitol hexanitrate, isosorbide dinitrite and trinitrite, have still longer duration of action. They are all fairly toxic and can produce methaemoglobinaemia, nitrite syncope and also tolerance. They are used in angina pectoris, cyanide poisoning and in lead colic.

The *antiatherosclerotic agents* are usually the anticholesterolaemic drugs which act by (a) Decreasing the absorption—sitosterol, cholestyramine, neomycin (b) Inhibiting the synthesis—triparanil, nicotinic and farnesoic acids (c) Increasing cholesterol degradation—paritol and also (d) Miscellaneous agents—PAS, Vitamin A and aminopterin.

The *antihypertensive drugs* represent many groups—(a) acting centrally e.g. sedative hydralazine, mebutamate, (b) blocking afferent impulses to the C.N.S.—veratrum, (c) acting on the sympathetic ganglia—mecamylamine, pentolinium (d) acting on the sympathetic nerve endings by depleting catecholamines—reserpine, guanethidine, alpha methyl dopa (e) by inhibiting their release—MAO inhibitors and (f) affecting vessel musculature and extracellular fluid—nitrites, aminophylline and thiazides.

The *therapy* of hypertension, though better than in the past, is still very complex. In *mild* cases, besides phenobarbitone sedative, chlorthiazide and reserpine are all that is required. In *severe* cases, chorthiazide, mecamlamine, ansolysin, guanethidine, veratrum alkaloid and methonium compounds, should be tried.]

The chapter comprises several groups of drugs discussed in different sections. However, as ultimately their actions, though differing in nature, refer to the blood vessels, special and general, it is advisable to group them under one head, in this chapter, under the following three sub-headings—(a) Vasoconstrictors (b) Vaso and coronary dilators and (c) Antiatherosclerotic agents.

VASOCONSTRICTORS

A large and diffuse group of drugs, acting through diverse mechanisms and producing constriction of blood vessels, with consequent rise in blood pressure. They are useful in hypotensive and shock-like conditions.

CLASSIFICATION

Acting on the V.M. Centre.	Caffeine, nikethamide, leptazol, CO ₂ .
Acting on the Sympathetic Ganglion.	Nicotine (small doses).
Acting on the Adrenergic receptors.	Adrenaline, noradrenaline, ephedrine, neo-synephrine, mephenteramine, dexedrine, privine, methedrine, vasoxyyl.
Acting on the smooth muscles.	Vasopressin, adrenochrome, conjugated oestrogens, angiotensin.

Most of these drugs have been studied in their respective chapters. Their principal action results in vasoconstriction, permitting increased blood volume in general circulation and thus preventing peripheral vascular failure. The actions however are of short duration and of a palliative nature for tiding over a state of emergency. Their important *uses* are—

1. Hypotensive States: (a) *After spinal anaesthesia.* There is often a fall in blood pressure because of the paralysis of the sympathetic transmission. The drugs most commonly used are vasoxyyl, methedrine, mephenteramine and in severe cases, noradrenaline.

(b) *Anaphylatic shock.* This is a severe and sudden allergic manifes-

tation seen with drug like penicillin. Besides hypotension, there are dyspnoea and other allergic symptoms, possibly because of histamine release. The drug of choice is adrenaline which has prompt action and also antiallergic effect.

(c) *Peripheral circulatory failure due to haemorrhage, fluid loss and surgical shock.* In these conditions, the fall of blood pressure occurs from either reduced blood volume or increased capacity of the circulatory bed, because of vasodilatation from sympathetic paralysis. Subsequent to this as a compensatory phenomenon, intense vaso-constriction takes place in order to maintain the blood pressure. However, if the vasoconstriction is excessive, anoxia may occur in the vital organs and venous return to the heart is reduced, resulting in a reduction in cardiac output and further fall of blood pressure. This leads to further anoxia and the arterioles also may dilate, causing more fall of blood pressure. Thus a vicious circle may set in. The condition should be immediately treated not by giving vasoconstrictors which have a tendency to aggravate the tissue anoxia but by replacing the fluid loss and then giving adrenergic alpha receptor blocking agents, like phenoxybenzamine, which by reducing the sympathetic effect on the blood vessels, cause dilatation and increased blood supply to the tissues. However, in early cases, vasoconstrictors may be used to temporarily maintain the blood pressure when fluids are being replaced and so also in advanced cases where the vessels have dilated.

(d) *Cardiogenic shock.* It occurs in cardiac conditions, like coronary thrombosis where the defect weakens the myocardium resulting in decreased cardiac output and hypotension. The obvious choice is a drug which will be a myocardial stimulant and not merely a vasoconstrictor. However even a myocardial stimulant cannot be used carelessly, because the heart is damaged and its oxygen supply is reduced. Further most of the sympathomimetic cardiac stimulants, excepting mephenteramine, are liable to induce arrhythmia in these patients. The commonly used drugs are—metartrinol, mephenteramine and sometimes a slow infusion of noradrenaline.

(e) *Vaso vagal attack.* In this, there is a sudden fall of blood pressure with syncope, due to increase in vagal activity. Although vasoconstrictors may help, the right drug is atropine which acts by blocking the vagal activity.

2. Haemostasis: For the local arresting of bleeding, as in epistaxis, a pack soaked in adrenaline (1/1000 sol.) may be used. Adrenochrome and conjugated oestrogens are also used sometimes, by the parenteral route.

3. Nasal Decongestion: The drugs preferred for this are privityne and benzedrine.

4. For prolonging the effect of local anaesthetics. Adrenaline and pitresin are used. The former has the disadvantage that by increasing the tissue oxygen requirement, it can cause necrosis.

VASODILATORS

Like vasoconstrictors, this is again a diffuse group of drugs which bring about vasodilatation by different mechanisms. They find their use in a number of conditions. *Pharmacologically*, they can be classified as under:

C.N.S. depressants.	Cerebrum—general anaesthetics, alcohol. Hypothalamus—reserpine, hydrargine, hydralazine (apresoline). Vagal ganglion—veratrum. Spinal cord—spinal anaesthetics.
A.N.S.	Sympathetic ganglion—methonium and other ganglion blockades. Sympathetic post-ganglionic nerve endings—reserpine, syrosin-gopine, guanethidine, L-methyldopa, bretylium.
(a) Depressant. (b) Stimulant.	Adrenergic receptors—sympathetic blockades, isoprenaline Cholinergic receptors—acetylcholine.
Smooth muscles.	Nitrites, papaverine, aminophylline, nicotinic acid, histamine and khellin.

Vasodilators may also be classified depending on their *therapeutic uses*:

Coronary diseases.	Nitrites, aminophylline, papaverine, khellin, nicotinic acid and alcohol.
Hypertension.	Rauwolfia, hydrargine, apresoline, veratrum, ammonium compounds, nitrites, xanthine, nicotinic acid, papaverine, guanethidine, α -methyldopa.
Vascular diseases.	Priscoline, dibenamine, ergot, ammonium compounds, nicotinic acid.

CORONARY DILATORS

General Considerations: In spite of all advances, the physio-pharmacology of the coronary vessels still remains an enigma. This is because, like the heart, the coronary vessels present great complexities in functional, as well as pharmacological studies of drug action.

The pattern of distribution of the right and left coronaries has species, as well as, variation in respect of anastomosis within the muscle bundle fibres and it is not definitely known whether some of them are new formations or dilatations of patent vessels. Coronary venous return takes place through the sinus, anterior cardiac vein and through thebatic and luminal vessels and therefore, study of outflow through the sinus only, as is often done, is not a complete measure of the coronary inflow. Further, coronary flow is affected by changes in the circulatory haemodynamics, aortic pressure, cardiac rate, extravascular compression, venous tone and also hypoxia.

The myocardial oxygen consumption value and coronary flow also run parallel. In ventricular fibrillation O_2 usage of the heart may be reduced to 3.2 ml % in place of 12-14 ml per minute.

The neurohumoral control of the coronaries through the sympathetic and parasympathetic systems, as well as through the local hormones—histamine, serotonin and bradykinin, is often ill-defined and sometimes contradictory and much of the effects observed on the coronary bed, may be either primary or secondary actions.

Pharmacological Considerations: In view of all these, pharmacologic responses of the coronaries by the available techniques of heart *in situ*, Langendorff method, heart-lung preparation, isotopic studies, all present intrinsic difficulties in the accurate evaluation of drug action.

Clinically, coronary insufficiency affecting nutritional supply to the cardiac muscles, results from two main conditions—(a) angina pectoris and (b) myocardial infarction. As both of them are accompanied by the alarming symptom complex of an impending death, drug therapy for immediate relief and further alleviation, demands the use of effective and dependable agents, from out of those available at present, for their treatment.

NITRITES

The nitrites constitute major therapeutic agents as coronary and general vasodilators and are commonly used in coronary insufficiencies of the type of angina pectoris. They comprise both NO_2 and NO_3 radical-bearing nitrite and nitrate compounds, commonly known as nitres. Some of the compounds are old, others new and several have been added very recently. Nitroglycerine was discovered in 1847, amyl nitrite in 1867, mannitol hexanitrate in 1894, sodium nitrite in 1897, octyl nitrite in 1938, isosorbiate in 1939, triethanol in 1940, and pentaerythryl tetranitrate in 1944. Of these, the oldest is still the most used but an ideal preventive and curative drug, has yet to be found out.

PARTICULARS AT A GLANCE

INORGANIC.	Sodium nitrite.	Tab.—60 mg/OS.	Unstable, rapid action
	Bismuth subnitrate.	Tab.— 2 gm/OS.	Stable, slow action.
ORGANIC.	Amyl nitrite.	Cap.—0.1-0.3 ml/Inhl.	Volatile, Capsule is to be crushed between cotton pledgets and inhaled. Very quick and short action.
	Octyl nitrite.	Cap.—0.2 ml/Inhal.	Stable but quick and short action. Mode of use as above.
	Glyceryl trinitrate.	Tab.—0.4 mg/Subling.	Liquid explosive but not tablet. To be crushed between the teeth before swallowing.
	Erythrityl tetranitrate.	Tab.—30 mg/Oral.	Slow and prolonged action.
	Mannitol hexanitrate.	Tab.—30 mg/Oral.	Stable, slow and prolonged action.
	Pentaerythrityl tetranitrate.	Tab. —10-20 mg/Oral.	—do—
	Isosorbide dinitrate	Tab.—10 mg/OS, Subling	- do—
	Trinitrate phosphate.	Tab.—2-4 mg/O.S.	—do—

The nitrites thus belong to 3 *distinct groups* according to their onset and duration of action, for *clinical uses*:

1. *Short acting* — Amyl and octyl nitrites.
2. *Medium acting* -- Nitroglycerine and sodium nitrite.
3. *Long acting* — Erythtrityl tetranitrate, pentaerythrityl — tetranitrate, mannitol hexanitrate, triethanol

Actions: The cardinal pharmacological action of nitrites is only one direct musculotropic antispasmodic action on plain muscles, without any central or peripheral nervous mechanisms. The tone of smooth muscles is reduced but their ability for maximal contraction remains unimpaired on stimulation.

C.V. System. Dilatation of post-arteriolar small blood vessels, capillaries and also veinules.

(a) *Skin vessels* are dilated by amyl nitrite forming *blushing zone* on the face and the neck, up to the clavicle. Sodium nitrite does not produce this effect.

- (b) *Meningial vessels* — dilated. Consequent headache and cephalgia after amyl nitrite and erythrityl tetranitrate.
- (c) *Splanchnic vessels* are dilated and the organ volumes observed to be increased in plethysmographic studies.
- (d) *Coronary vessels* are markedly dilated and this is the basis for their use in angina pectoris. Experiment of Essex (1940) with thermostromuhr showing 30—100% increase in coronary blood flow after nitroglycerine.
- (e) *The retinal vessels* — are also dilated.
- (f) There is a marked fall of the systolic and less of the diastolic pressure. The pulse pressure is diminished.

<i>Preparations</i>	<i>Onset of B.P. fall/ minute</i>	<i>Maximum/ minute</i>	<i>Fall mm. Hg.</i>	<i>Recovery/ minute</i>
Amyl nitrite	$\frac{1}{2}$	3	25	8
Nitroglycerine	1	10	30	40
Sodium nitrite	5	40	40	150
Erythrityl tetranitrate	15	50	40	300
Mannitol hexanitrate	15	120	40	360

Heart: The stroke volume is reduced by 15%. There is tachycardia and improved blood supply to the organ. The pulse is full and dichrotic and the electrocardiogram is normal.

Smooth Muscles: of bronchioles, biliary, G.I. and G. urinary tracts—are all relaxed and the intrabiliary pressure is reduced. There is thus a marked antispasmodic effect on all the plain muscles of the body.

Special Features: (a) *Amyl and octyl nitrites* have prompt but short action (a few minutes only) and are used by inhalation for aborting or relieving the acute anginal attacks.

(b) *Nitroglycerine* — the liquid being explosive, *tablets* of 0.5—1 mg. are used sublingually as a preventive. Its action starts in 2—3 minutes and lasts for $\frac{1}{4}$ hour.

(c) *Sodium nitrite* — the solution being unstable, it is used in tablet form — 30—120 mg/o.s. as a prophylactic. Its action starts in 15 minutes and lasts for 1 hour. It is not well tolerated as it causes gastric upset and vomiting.

(d) All the *longer acting*, tetra and hexanitrate, are explosive in pure states but in the form of tablets, they are used as prophylactics for angina and sometimes also in hypertension. Their

action starts in about an hour and lasts for several hours, because of their slow absorption from the gut. *Dose*: 15 -- 30 mg/os. They effectively dilate the coronary vessels and also reduce systemic blood pressure.

- (e) All the nitrites induce appreciable tolerance on prolonged use and this does not refer only to the long acting ones.

Side-Effects: They are usually associated with overdoses and prolonged uses of these drugs as vasodilator or otherwise. The major conditions are two—(a) *Methaemoglobinaemia* and (b) *Nitrite syncope* — detailed elsewhere.

The *first* is produced more frequently by sodium nitrite, nitroglycerine and also bismuth subnitrate, which last, is used in the treatment of diarrhoea in children. The *second* which occurs in sensitive individuals, is an alarming condition, though not necessarily fatal and is produced more often by glyceryl trinitrate. There is considerable peripheral vasodilatation, specially on standing.

The venous return to the heart falls, the cardiac output drops and the circulatory volume is greatly reduced. This results in cerebral anoxia, syncope and collapse. There is nausea, vomiting, pallor and cold sweating. Patients usually recover in an hour. Adrenaline is not always effective and atropine should also be used.

Uses: (a) *Angina pectoris*: both preventive and palliative.

(b) *Hypertension*: doubtful result. Use even of long acting ones is controversial.

(c) *Asthma*: Adrenaline, ephedrine or theophylline preferred.

(d) *Pylorospasm and lead colic*: adequate relief.

(e) *Cyanide poisoning*: useful.

OTHER DRUGS

They comprise -- (a) Papaverine and related compounds -- ethaverine, dioxyline phosphate, trimethylcyclohexanyl mandelate, dipyramide, profenil and dibutamide; also sestron, nicotinic acid and b-pyridol carbinol. (b) Khellin and aminophylline -- possess papaverine like activity.

Papaverine: The benzyl isoquinoline alkaloid of opium, causes direct relaxation of smooth muscles including the coronaries and has a prolonged action. It depresses the conduction and irritability, increases the refractory period and renders the myocardium less sensitive to stimuli, for causing arrhythmia. It dilates the pulmonary, cerebral and peripheral arteries and stimulates the respiration. It is sometimes

used in angina pectoris, coronary infarction and in embolism of the pulmonary vessels, several times a day. Tablets of 100 mg/o.s. t.d.s. are used as prophylactic for angina pectoris. *Ethaverine and dioxyline* PO_4 — the tetraethyl homologue of papaverine, are chemically related to it. Its actions are similar to those of papaverine but more potent and less toxic. *Trimethylcyclohexanyl mandelate*—an ester of mandelic acid, which has also papaverine-like activity, and is used in peripheral vascular disease, spastic conditions of viscera and as coronary dilator in angina pectoris. *Dose*: 100 mg. t.d.s. *Dipyramidole* — a complex derivative of pyrimidine, having papaverine like activity, though less marked on peripheral arteries. The vasodilatory action is indirect, due to accumulation of adenosine in the heart, caused by the inhibition of adenoside deaminase. It also raises the A.T.P. level in the heart muscle and improves its blood supply. *Profenil* — a more potent direct relaxant of smooth muscles, used for relieving the spasm and pain in gastric ulcer and in spasmodic colitis. *Dibutamide* — has a selective action on the uterus and is used in dysmenorrhoea. It antagonises smooth muscle contractions. *Sestron, nicotinic acid and b-pyridol-carbinol* — they cause dilatation of the small arteries arterioles and capillaries. *Khellin* an Egyptian drug, believed to be a coronary dilator, but now seldom used. *Dose*. Tabs of 40 mg. 1-4 tabs/day.

Aminophylline: A compound of theophylline with ethylene diamine which has a number of important actions and uses. The important *actions* are — (a) dilatation of coronary arteries, (b) stimulation of myocardium — direct action, (c) stimulation of respiratory and vasomotor centres, (d) relaxation of peripheral blood vessels, (e) diuretic action, (f) increased cardiac output, stroke volume and reduction of venous pressure in C.C.F. with oedema. *Dose*: (a) 100 — 500 mg. I.V., slowly, (b) When given by mouth, it causes G.I. disturbance, nausea and vomiting. Therefore, it is given with dried aluminium hydroxide gel, (c) I.M. injections are painful and may cause hypotension, syncope, headache and nausea.

Uses: Though there is some controversy about the clinical value of the xanthine in coronary artery diseases, it is still very widely used in some of the following conditions — (a) coronary infarction (b) angina pectoris (c) cardiac asthma (d) bronchial asthma (e) biliary colic and (f) as a diuretic.

These new drugs, with the exception of aminophylline and papaverine have yet to establish their comparative therapeutic status after more extensive clinical trials.

ANTIATHEROSCLEROSIS AGENTS

Cholesterol Metabolism: Atherosclerosis is one of the leading causes of death in many countries. The occlusion of blood vessels is considered to be responsible for coronary, cerebrovascular and peripheral vascular diseases. Experimental and clinical evidences suggest that there is a relationship between atherosclerosis and the concentration of lipids in the plasma. It seems to be a metabolic disorder, caused by the faulty absorption, transport, distribution and deposition of lipids. Diet, heredity, sex, stress and metabolic diseases are some of the other contributory factors. The concept of hypercholesterolaemia leading to the atherosclerosis, is one of the hypothesis.

Food lipids: A lot of work has been done on food constituents, particularly in respect of food lipids. Addition of vegetable oils, containing a large amount of unsaturated fatty acids to the diet or their substitution for foodstuffs, containing a high proportion of saturated fatty acids, has been found to lower plasma cholesterol level. Corn, cotton seed, soya bean and safflower oils, have been used for this purpose. Deaths from coronary, cerebral and pulmonary thrombosis, seem to have been reduced by replacing butter and lard, with corn and soyabean oils, in the diet.

Anticholesterol Drugs: Use of agents to reduce serum cholesterol level, is based on the finding that cholesterol content and atherosclerosis are related. Drugs can affect the blood cholesterol level by (a) decreasing the absorption, (b) depressing the synthesis and (c) increasing its degradation.

The synthesis of cholesterol is a complex process, involving many steps which can be affected by drugs at different levels, though not fully effectively.

Acetate \longrightarrow acetyl CoA \longrightarrow mevalonate \longrightarrow squalene \longrightarrow cholesterol

The drugs which are used for reducing hypercholesteroleamia are the following:

CLASSIFICATION

Agents Decreasing Intestinal Absorption	Sitosterol, cholestyramine, neomycin.
Drugs Inhibiting Lipid Synthesis	Triparanol, nicotinic and farnesoic acid cholest, non-benzamalacene, heparin, potin (Clarín)
Agents Increasing Cholesterol Degradation	Paritol, thyroxine and other analogues.
Miscellaneous	PAS, Vitamin A, aminopterin

Sitosterol (Cylellin): A plant sterol which differs chemically from cholesterol only by the presence of C_2H_5 at C_{24} position. It is used as competitor for the intestinal absorption-transfer mechanism of cholesterol, thereby reducing the absorption of exogenous cholesterol and resulting in hypocholesterolaemia. It is available as 20% suspension and given in 10 gm/day in divided doses, before and after the meals. It is used for the reduction of hypercholesterolaemia in diabetes mellitus, hypothyroidism and nephrosis.

Cholesteramine: A polystyrene-based anion exchange resin, capable of binding bile acids, which are required for cholesterol absorption. Its inhibition produces hypocholesterolaemic effect. *Dose:* 15 gm. daily. Average reduction in serum cholesterol level is 20%. Its side-effects are gastrointestinal distress, constipation and nausea.

Triparanol: A derivative of triphenylethylene, it is a specific inhibitor of cholesterol biosynthesis after the formation of the steroid nucleus. It leads to the accumulation of demesterol. *Dose:* not exceeding 250 mg/day. Because of its side-effects of skin reactions, loss of hair and cataract formation, the drug has been withdrawn.

Nicotinic acid: It interferes with the function of the coenzyme A, which is responsible for the synthesis of cholesterol. The enzyme action gets diverted to the detoxication of nicotinic acid, leading to the inhibition of cholesterol formation. This is supported by the fact that both the phenyl butyric and diphenyl butyric acids which require coenzyme A, for their detoxication, also block cholesterol biosynthesis. Reduction of cholesterol level in hypocholesterolaemic patients is more marked than in normal individuals. It interferes with the biosynthesis of cholesterol in liver. *Dose:* 3-6 gm/day. The side effects are pruritis and flushing.

Farnesoic acid and benzmalecene: They block cholesterol synthesis by acting as antimetabolites. The latter inhibits the incorporation of mevalonic acid into cholesterol and the sodium salt has been found to produce a reduction of cholesterol level by 29 to 30%, in feeding experiments.

Heparin: The activation of lipoprotein lipase with heparin and subsequent degradation of the large lipoprotein molecules, is responsible for the diminution of cholesterol in the blood. This has led to its use in the various types of blood lipid abnormalities.

Paritol: A purified preparation of sulphated polyanthranic acid which produces its effect, both by the activating of the lipase and also by a stimulation of the reticuloendothelial system. *Dose:* 2.5 mg/kg I.M. or I.V.

Thyroid hormone: Though it lowers the serum cholesterol level by

stimulating the degradation of cholesterol, its side effects have prevented its use in hypercholesterolaemia. Thyroxine analogues like dextro-thyroxin and D-triiodothyronine have however been used for reducing the blood cholesterol level in doses of 2-8 mg. PAS: has been found to reduce cholesterol level by 10 to 30% in a dose of 5-8 gm/day.

Vitamin 'A': 100,000 units/day/os for 4-6 weeks has also been observed to reduce the blood cholesterol level.

The above is a brief outline of the present position of our knowledge in respect of cholesterol metabolism, atherosclerosis and cholesterol antagonists in the body. This knowledge is still insufficient and until the pathogenesis of atherosclerosis is better understood, no effective therapeutic measures could be possible.

ANTIHYPERTENSIVE AGENTS

General Considerations: Hypertension has been a real enigma since the earlier days of our medical history and in spite of all advances in medicine and therapeutics, not only that it still continues to be so but what is more alarming is that its incidence seems to be much on the increase.

It was believed that there was probably an ethnic, environmental factor related to its causation inasmuch as, in underdeveloped countries, the normal blood pressure level, as well as the incidence of hypertension, was much lower. It has however been observed that the African negroes living in U.S.A., showed $2\frac{1}{2}$ times greater incidences of hypertension than the native white population. This seems to indicate that other factors like mode, stress and strain of modern life, food habit and impacts of modern civilization, play even a greater role than probably the racial factor, in the causation of this condition.

In hypertension, the systolic pressure which is directly related to the cardiac output, is of lesser importance than the diastolic, which is indicative of the peripheral resistance. Normally, in a middle aged person, a B.P. of 155/95 is considered to be the upper normal limit.

Pathogenesis: Though the factors regulating the maintenance of the normal B.P. is fairly established, this is not so, so far as the pathogenesis of hypertension is concerned. There are two principal types of hypertension. The *Primary or essential hypertension* is without any kidney damage, or any other apparent cause while, the *Secondary hypertension* is associated with pyelonephritis, chronic nephritis, Cushing's syndrome and several other diseases. With advanced knowledge of medicine and therapeutics, the incidence of secondary hypertension

has much decreased and it is the essential type, which now constitutes nearly 90% of cases of hypertension.

Primary Hypertension: Though very little is still known about its pathogenesis, there is considerable arteriolar constriction, associated with a degree of C.N.S. and psychological upset, induced by conflict, stress and tension, resulting in:

- (a) Increased activity of the vasoconstrictor centre, due to derangements in the functioning of the hypothalamus.
- (b) Increased secretion of posterior pituitary hormone-vasopressin, which constricts the vessels.
- (c) Increased ACTH secretion causing stimulation of secretion of DOCA, resulting in sodium retention and rise of blood pressure and
- (d) Increased stimulation of adrenal medulla and secretion of adrenaline.

Consequent to recent studies, the role of pressor amines in the etiology of hypertension is becoming increasingly apparent. It is now believed that nor-adrenaline is stored in the walls of the blood vessels and can easily be released, causing vasoconstriction. Similarly, the pressor responses of epinephrine have been found to be augmented in animals, pretreated by mineralcorticoids. The likelihood of sensitisation of the adrenergic system by stress mechanisms, as a cause of hypertension, appears to be plausible. Scrotonin, which is a pressor amine, may also play an important role in this mechanism.

Renal Hypertension: Whenever blood supply to the kidney is reduced, it tries to check ischaemia by raising blood pressure after secreting an enzyme *Renin*, which hydrolyses globulin hypertensinogen produced by liver, into hypertensin, which is a vaso-constrictor factor. This theory holds good only in the initial phases of hypertension as *renin* has not been detected in the blood of long standing cases of renal hypertension.

Evolution of Drug Therapy: The treatment of hypertension which has been greatly handicapped by lack of precise knowledge about the causation of the disease, is essentially symptomatic. Hypertension basically is an attempt on the part of the body to maintain the circulation through diseased vessels. To that limited extent, it is a necessary compensatory phenomenon. However, it is the deleterious effects that any continued and severe hypertension has on the integrity of the blood vessels and the vital organs like eyes, kidneys and brain, that prompts the

physicians to lower the blood pressure, only to the extent that is essential.

In the first quarter of this century, there was hardly any antihypertensive drug of importance. The few that were available were either ineffective, short acting, toxic or producing tolerance. A major breakthrough was made in the forties with the introduction of adrenergic blocking and a little later of the *ganglion blocking agents*. In less than 20 years, even some of these have become partly obsolete, and we have not only a larger number of better drugs now, but also a greater awareness of the physiopathological mechanisms of the disease in the designing of better drugs.

Development of *modes of study* of antihypertensive drugs, started in the early fifties, with the introduction of *Rauwolfia serpentina* as an antihypertensive agent. In 1958, a new *diuretic-chlorothiazide* was discovered which had antihypertensive action also.

In 1959, a new class of drugs, capable of blocking the effects of the sympathetic nerve stimulation, was discovered. Among them, *guanethidine* holds a prominent place. After this, a large number of *enzyme inhibitors* - - decarboxylase and monoamine oxidase inhibitors, which too have antihypertensive properties, have been discovered. Another new antihypertensive, acting on the central mechanisms, is *mebutamate*, which is a derivative of meprobamate, a tranquilliser.

The inevitable outcome of all these has been the general rejection of drugs which once served physicians in their humble capacity. Adrenergic blockade — dibenamine, smooth muscle relaxant — nitrites, thiocyanates have all played their roles and have almost retired from the routine therapeutic field of hypertension, at present.

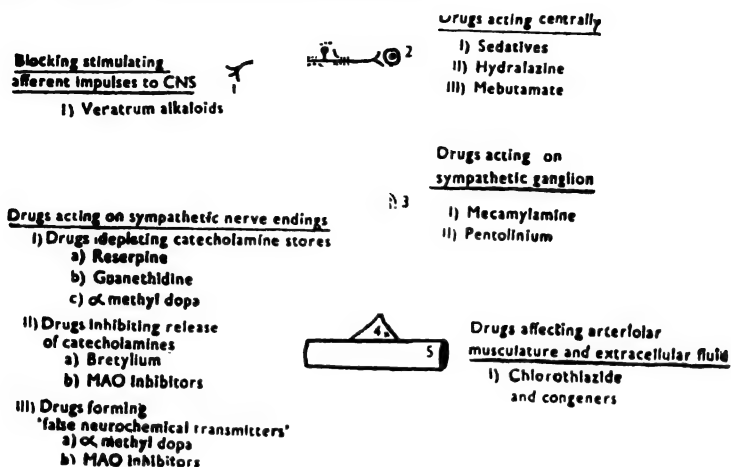
The currently available antihypertensive drugs often have multifaceted sites of action—hydralazine acting on brain stem centres, as well as on peripheral pherantasin mechanism. A general scheme, showing the principal sites of action of drugs, commonly used in the therapeutics of hypertension, is diagrammatically represented in *Illus. XVI* (overleaf).

Methods of Screening: The complex mechanisms of antihypertensive action of different groups of drugs reflect on the complicated nature of this disorder. Though several methods for the screening of these drugs as detailed below, are available, they cannot be considered to be highly satisfactory. Some of the techniques in use are:

(a) Assessment of hypertensive effects on the normotensive laboratory animals—dogs, cats and others and also after the induction of

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acute hypertension in these animals by the slow perfusion of catecholamines through a microinfusion pump.



Illus: XVI. Sites of action of antihypertensive drugs

(b) Induction of chronic hypertension by (i) Goldblatt's method of induction of renal ischaemia by the compression of renal vessels, (ii) Decapsulation and cellophane paper technique also for the same.

(c) Induction of experimental atherosclerosis in pigs and other animals.

(d) Clinical evaluation of effects of drugs in hypertensive patients.

None of these however produce hypertension simulating the clinical ones and this is a limitation for the correct assessment of antihypertensive drugs, at the present stage of our knowledge.

RAUWOLFIA SERPENTINA

A tropical shrub growing in DehraDun, Bihar and Bengal regions of India, which in recent years, has established the reputation of a wonder drug and set in motion many interesting pharmacological, biochemical and clinical studies. It belongs to the family of apocynaceae and the root contains a series of alkaloids, collectively known as 'indole derivatives! The important alkaloids are (a) reserpine, (b) ajmaline, (c) serpentine, (d) rescinnamine etc. Serpina tablet made with the root powder, is also sometimes used.

Though a lot of work on this plant was carried out in India from the earlier thirties, by Chopra, Bose, Siddiqui, Vakil and others, of late,

extensive chemical, pharmacological and clinical research have been carried out by Bein and others and its status as a drug, as well as a pharmacological tool, is fully established.

Reserpine: possesses the unique property of hypotensive and tranquillising actions and finds its important uses in cases of hypertension and of the mentally ill and many other conditions. The drug has been detailed in the chapter of psychopharmacology.

(a) Pharmacologically, reserpine has not been found to evoke any peripheral adrenolytic or parasympathomimetic activity, nor any blockade in the transmission of autonomic ganglia.

(b) It increases gastric secretions and G.I. tract activity, which may be due to the central sympathetic preponderance at the level of the hypothalamus where autonomic balances are integrated. The secretory effect is not always constant.

(c) Reserpine also affects the temperature regulation through its hypothalamic action and elicits sedation, myosis, bradycardia and relaxation of peripheral blood vessels which may be due to parasympathetic predominance resulting from the inhibition of the hypothalamic sympathetic activity.

(d) The hypotensive action is likely to be mediated at a higher level in the brain than the medulla and is due to the diminished sympathetic predominance. The release of norepinephrine from the brain, heart and arterial walls by reserpine is established.

(e) The drug is rapidly metabolised, about 30-40% appearing in the urine within 4 hours as trimethoxybenzoic acid. Fecal excretion is only 8% of the oral dose.

Syrosingopine—Carbethoxy springoyl methyl reserpate, is a synthetic derivative of reserpine possessing the same type of responses as of reserpine, with the exception that it has mild calming effect on the brain. The action is primarily peripheral causing an inhibition of the flow of sympathetic impulses to the arteries, by depleting noradrenaline from the nerve endings. It has also a central serotonin releasing action, in the brain. Unlike reserpine, it has much less side-effects. *Uses*: In *mild* hypertension; 0.25 mg 3 or 4 times a day and in *severe* cases, 1 mg 4 times a day.

BRETYLIUM TOSYLATE

Darenthin is a quarternary ammonium compound which is said to selectively accumulate in the sympathetic nerve endings and due to its strong local anaesthetic action, it does not allow sympathetic nerve impulses to travel and release catecholamines, thus producing sympa-

tholytic action. Unlike adrenergic blocking agents like Priscol, it does not block the effects of the circulating catecholamines. The drug has been used alone or with other hypotensive drugs, in doses of 200 mg. t.d.s./os.

Its repeated administration, however, leads to the reduction of stores of catecholamines, as well as, increasing the tolerance to the drug. Consequently, it has almost been withdrawn from use as any good antihypertensive agent. Further, the hypotensive action has also a short duration of action.

Its disagreeable effects are—muscular weakness, nasal stuffiness and postural hypotension.

GUANETHIDINE

It is a guanidine derivative with apparent sympatholytic action similar to bretyllium but the actual mechanism is somewhat different. It does not have any local anaesthetic action. It is said to cause the release of catecholamines from the stores at a rate much faster than the synthesis, resulting in the emptying of stores after sometime. An incoming sympathetic nerve impulse then fails to cause vasoconstriction. Recent work also suggests that guanethidine forms a barrier which prevents an incoming nerve impulse from causing catecholamine release, even though the stores may not have been completely empty. The fall of blood pressure caused by guanethidine is mainly in the erect and much less in the supine position. All the reflex pressor responses are also blocked by guanethidine.

Guanethidine is a potent antihypertensive agent, with a long duration of action and has a place when used in conjunction with other hypotensive drugs or alone in the treatment of severe type of hypertension. Usually, no tolerance is formed. The side effects are (a) Diarrhoea and bradycardia from the parasympathomimetic action which is blocked by atropine. (b) Nasal stuffiness and general weakness as with bretyllium. (c) Further, troublesome postural hypotension and failure of ejaculation, due probably to its sympathicosthenic action.

The drug is available as 10 mg. tablets, the treatment starting with $\frac{1}{2}$ tablet a day and slowly raised till an appropriate response is obtained.

ALPHA METHYL DOPA

The introduction of this drug has heralded a new concept of antihypertensive therapy. It is a decarboxylase inhibitor and is supposed to prevent the conversion of dopa to dopamine, ultimately resulting in

the less formation of noradrenaline. As methyl dopa competes with dopa for the enzyme decarboxylase the methyl dopamine, instead of dopamine, is formed. From the former, methyl noradrenaline is formed and this replaces noradrenaline from the stores. When a nerve impulse comes through the sympathetic nerve instead of noradrenaline, a much weaker pressor agent is released, resulting in the attenuation of sympathetic effects. This is known as "the false neurochemical transmitter hypothesis". Besides its action on the catecholamines, 1-methyl dopa also prevents the synthesis of 5HT and this is believed to be an explanation for the transient initial sedation, produced by 1-methyl dopa. After continued use for 6 hours, the sedation disappears and the hypotensive action occurs.

This drug, which is intermediate in potency to reserpine and guanethidine, causes less postural hypotension. It is useful in moderate hypertension, not responding satisfactorily to the reserpine therapy. It is available as 250 mg. tab. 2 tabs/day, increased by 1 tablet every 3rd day, till an adequate result is obtained.

The side-effects are—drowsiness, mental depression, nasal stuffiness, impotence, vertigo, congestive cardiac failure and raised serum bilirubin. Usually no tolerance is formed.

HYDRALAZINE

Also known as *apresoline*, it was initially synthesised as an antihistaminic, containing a hydrazine group. It was subsequently found to be a long acting vaso-depressor with its site of action, primarily at the level of the arterioles. It inhibits dopa decarboxylase and histidine decarboxylase enzymes and inactivates pherentasin and angiotensin. The vasopressor action elicited by adrenaline, noradrenaline, histamine, vaso-pressin and barium, is antagonised by hydralazine which suggests that the action is direct on the arterioles. The drug also possesses chelating properties and the mechanism of its action may be due to the chelation of metals, which are parts of some enzymes.

Dose: Apresoline hydrochloride:—Tablet of 10, 25, 50 and 100 mg., initial oral dose—10-25 mg. 6 hours, increased by 10-25 mg every 7 days, the total oral dose not exceeding 400 mg. daily. Apresoline hydrochloride solution 20 mg/ml: 20-40 mg. I.V. or I.M. every 4-6 hrs. may also be used. The drug is well absorbed from the G.I. tract and the maximal blood levels are reached within 1-3 hrs. of the oral administration. Most of it is metabolised and excreted.

Action: The hypotension is produced by peripheral vasodilatation with a marked reduction in the total peripheral resistance. It increases the cardiac output by causing an increase in the heart rate and stroke volume.

There are many *side-effects*: (a) Nausea, vomiting, colic pain, diarrhoea and localised oedema. (b) Headache, dizziness, postural hypotension. (c) Palpitation, tachycardia, angina and myocardial infarction. (d) Development of collagen disease—lupus erythematosus, which is reversible after the stoppage of the drug.

Uses: They are quite limited. The drug may be given in combination with other hypotensive drugs like reserpine and guanethidine when considered absolutely essential.

MEBUTAMATE

Also known as *Capla*, it is chemically closely related to meprobamate and is used for the treatment of mild hypertension. It has no effect on the autonomic nervous system and its hypotensive action is due to a direct depressant effect on the V.M. centre, causing reduction in the peripheral vascular resistance. The side effects are drowsiness, headache xerostomia, nasal congestion, constipation and weakness.

THIOCYANATES

Though sodium and potassium salts are available, the preparation in use is—Elixir sodiumthiocynate—4% (0.3 g/daily for—3 days: and then 0.3 g/weekly.)

Actions: (a) It is believed to have the actions of nitrites and iodides, giving sympatomatic relief in essential hypertension, which is not amenable to other therapies.

(b) Its optimal therapeutic concentration is 8-10 mg. % but the toxicity consisting of fatigue, cramps, coryza, dermatitis, thyroid swelling and vascular collapse, occurs in a concentration of 12-14 mg. %. It has thus very narrow safety margin and is seldom used.

VERATRUM

There are two varieties of the plant the *viride* and the *album*, the active principles being a series of *alkaloids*: veratrine, veratridine, protoveratrine.

Actions; It produces vasodilatation by 'Bezold-Zarisch reflex', arising from the lung large vessels—vagus→V.M. centre thus antagonising accelerator action of adrenaline and producing veratrinic contractures in skeletal muscles.

Uses: It is an adjuvant to the reserpine therapy and is used only in (a) malignant hypertension, (b) hypertensive encephalopathy and (c) toxæmia of pregnancy.

Dose: Veriloid: 3 mg. tab: protoveratrine 0.5 mg tab/qds. This drug has narrow safety margin and has to be used with caution and in selected cases only.

THIAZIDE DIURETICS

A number of benzothiadiazine derivatives—chlorothiazide, hydrochlorothiazide, benzthiazide, polythiazide and methyl chlorothiazide, are endowed with diuretic as well as hypotensive properties. These oral diuretics possess two components of diuretic action: one by the inhibition of carbonic anhydrase in the renal tubule and acting in the presence of both acidosis and alkalosis and (b) the other similar to the mercurials. They help in the excretion of bicarbonate and potassium, as well as chlorides. Their hypotensive action is not due only to the diuretic action, as the former persists when the latter is stopped. Certain compounds in the series also possess the hypotensive action without sodium depletion.

Many mechanisms have been ascribed to their action: sodium, potassium and bicarbonate depletion with reduced turgescence of blood vessels, altering the electrolyte gradient between the extra cellular compartments and the peripheral resistance. Till the veil is lifted, it is better to believe that the thiazides act directly on the vessel wall, causing lowering of the peripheral resistance.

Their duration of action, varies from 6-48 hours; *chlorothiazide*—6 hrs; *hydrochlorothiazide*—12 hrs. and *polythiazide*—24 hrs.

In view of their mild action, they are used in *mild* and moderate forms of hypertension along with reserpine or in *severe* types, along with the ganglion blockades and veratrum. They also find their uses in CCF and cirrhosis with oedema. They show additive effects with the mercurials. Because of K depletion, they enhance the toxicity of digitalis and should not therefore be used together, as far as possible.

Side Effects: (a) hyponatraemia, (b) hypokalaemia and (c) hyperuricaemia.

THERAPEUTIC ABSTRACT

<i>Angina pectoris</i>	<i>Coronary thrombosis</i>	<i>Hypertension</i>		
		<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Amyl nitrite	Morphine or	Thiazides	Thiazides	Thiazides
Octyl nitrite	Pethidine		Reserpine	Mecamylamine
Long acting nitrites	Oxygen	Reserpine	Hydralazine	Ansolysin
	Noradrenaline		α methyl dopa	Ecolid
Phenobarbitone	Heparin or			Guanethidine
Theophylline	Dicumarol			Veritoids
Papaverine	Quinidine			

THERAPEUTIC CONSIDERATIONS

They refer principally to the following three important conditions:

(a) *Angina pectoris*, (b) *Coronary infarction* and (c) *Hypertension*.

Angina Pectoris: An alarming condition with intense coronary spasm, radiating pain increasing by exertion and cardiac hypoxia. The seizures last for few minutes only and reappear periodically.

For acute attack: Short acting nitrites—amyl nitrite, octyl nitrite and glyceryl trinitrite are used and the pain is relieved, instantaneously.

For the preventive therapy: (a) Phenobarbitone sedative along with (b) vasodilators—(i) theophylline, (ii) papaverine, (iii) khellin, (iv) nitrites—medium and long acting groups—sodium nitrite, erythryl tetranitrate and mannitol hexanitrate are made use of.

Some of the vitamins and hormones, testosterone propionate, nicotinic acid or niacin are also used as peripheral vasodilators.

Coronary Thrombosis: This condition is characterised by the formation of thrombosis inside the coronary artery leading to stoppage of blood supply to the heart and ischoemia of the cardiac muscle. As a result of this there are (i) severe pain in the chest, (ii) poor cardiac functioning causing a fall of B.P. and shock, (iii) leucocytosis, (iv) Increased level of S.G.O.T. and E.S.R. and (v) cardiac arrhythmia.

Treatment comprises (i) absolute bed rest (giving rest to the heart), (ii) morphine or pethidine (full dose) to relieve the pain and the shock, (iii) oxygen intranasally, (iv) vasopressors like noradrenaline and mephenteramine, (v) use of anticoagulants like heparin or dicoumarol (dindivan) and (vi) anti-arrhythmic drugs (quinidine or pronestyl).

The treatment has to be continued for a long time and generally 6-12 weeks are required for the recovery.

Hypertension: This is a fairly serious condition with far reaching implications on the long term positive health of an individual. Its incidences are alarmingly on the increase in every country and comparatively younger groups of persons are being affected. The incidence varies between 25-60% according to age groups between 35-70 years and the primary hypertension constitutes the majority of cases these days. Amongst the etiological factors, which are far from established. (a) endocrine, metabolic, A.N.S. imbalance, renal ischaemia, (b) increased circulating phrentasin, noradrenaline and serotonin and (c) obesity and climateric disturbances, have been incriminated.

Clinically, three degrees of hypertension based on the severity of the disease have been accepted:

1. *Mild:* In this, the diastolic pressure is taken as 100 mm Hg. There should be no cardiorenal involvement and only grade I fundal changes might occur.

2. *Moderate:* In this, the diastolic pressure could be about 110 mm. Hg. with some cardiorenal involvement but no azotaemia and grade II fundal changes could occur.

3. *Severe:* Here the basal diastolic pressure is above 120 mm. Hg. and cardiorenal decompensation and failure with grade III & IV of fundal changes are to be expected.

Treatment: Comprises —(a) general measures and (b) drug therapy.

General Measures: (a) Reassurance without provoking any B.P. consciousness, (b) Rest and restriction of activities, (c) Restriction of diet as required, and more important in obes persons with low salt and cholesterol diet, (d) Sedatives—phenobarbitone—15 mg. t.d.s. with 0.1 gm. at the bed time.

Drug therapy: Mild: (i) Chlorothiazide: 500 mg twice a day or reserpine: 0.5 mg/day for 2 or 3 weeks, subsequently reduced to 0.1—0.25 mg/day. If the response from either is inadequate, the combination of the two and then, recourse to other potent hypotensive-drugs, are indicated, specially when the condition is progressive.

Moderate: Initial drug therapy as in the mild variety. If more vigorous therapy is necessary, along with the diuretic, any of the following drugs may be added:

(a) Hydralazine—10 mg b.d. slowly increased to 25-50 mg. t.d.s. or q.d.s.

(b) Alpha methyl dopa: 0.5-1 gm/day, gradually increased to 3 gm/day

Severe: Hypotensive drugs are of value if any major irreparable

damage to the vital organs has not occurred. The objective is to reduce the diastolic pressure even at the cost of some discomfort.

(a) *Chlorothiazide*—500 mg. b.d. (b) *Mecamylamine*—2.5 mg. b.d. 10 mg. t.d.s. or *Ansolysen*—20 mg. tab 600 mg./day, till the desired effect has been obtained. (c) *Guanethidine*—10 mg/day, increased at weekly intervals, up to 500 mg./day, till the full effect has been attained. (d) *Methonium compounds*, bretylium and veraloids are either seldom used or used with a great deal of caution these days.

In spite of all these advances, the therapy of hypertension is still mostly of a palliative nature. Under strict supervision and with full cooperation of the patient, though much can be done to keep the patient relatively symptom-free with controlled B.P., with which he lives in mild and moderate cases, but the prospect of controlling the inexorably progressive course of the severe and malignant form of hypertension, with drug and other therapies, is not what can yet be legitimately claimed.

CHAPTER

31

DRUGS ACTING ON BLOOD AND BLOOD FORMING ORGANS

THE HAEMATINICS. R.B.C. AND W.B.C. STIMULANTS AND DEPRESSANTS.
COAGULANTS, ANTICOAGULANTS, SCLEROSING AND FIBRINOLYTIC
AGENTS. THEIR SCOPE AND LIMITATIONS

[Pharmacologic responses to blood and blood forming organs encompass divergent groups of therapeutic agents—the haematinics, stimulants and depressants of blood corpuscles and also coagulants, anticoagulants, sclerosing and fibrinolytic agents.

The haematinics which are intended for microcytic, as well as macrocytic anaemias, comprise iron, copper, manganese, vitamin B₁₂, folic acid, liver and stomach preparations. Of these, inorganic and organic irons as ferrous sulphate and saccharated iron oxide are the sheet anchors of iron deficiency anaemias, while vitamin B₁₂ and folic acid are used in macrocytic, hyperchromic anaemias.

A large number of chemical and physical agents depress W.B.C. forming organs producing leukopenia and agranulocytosis. Sulphonamides, chloramphenicol, butazolidine, organic arsenicals, amidopyrine, gold, other heavy metals, X-ray and radiomimetic substances, are some of them. For combating this serious condition, nucleic acid derivative-pentnucleotide and also folic acid and penicillin, along with blood transfusion, are used. In certain conditions, the number of R.B.C. and W.B.C. in blood are enormously increased. For the former, which is known as polycythaemia vera, P 32 and phenylhydrazine are used, while for the latter, cytotoxic, antimitotic and radiomimetic antileukaemic agents, discussed in the chapter of chemotherapy of malignancy, are used.

In certain diseases, when the normal coagulative processes of blood are at stake, the use of coagulants and anticoagulants are indicated. The coagulants comprise blood, thromboplastin, stypven, vitamin K, absorbable gelatin sponge, fibrin foam and oxidised cellulose, while the anticoagulants of importance are heparin and dicoumerol. The former has prompt and short effect, reversible by protamine and used in myocardial infarction, transfusion service and in vascular surgery. The latter has longer duration of action and reversible by vitamin K, in cases of toxicity hazards from any over-dosage.

The sclerosing agents are used in haemorrhoids and varicosis, and the fibrinolytic enzymes as physiological curettes for the cleansing of ulcers and wounds.]

Even after exclusion of *antileukaemic agents*, dealt separately under chemotherapy of malignancy of blood and other tissues the chapter

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comprises a large number of important groups of drugs, conventionally known as:

1. Haematinics or drugs acting in anaemias.
2. Drugs acting in polycythaemia and agranucytosis.
3. Drugs acting on blood coagulation processes — coagulants and anticoagulants.
4. Sclerosing and fibrinolytic agents.

These are old and new drugs which have added much to our knowledge of the physio-pathology of blood disorders leading to the discovery of increasing number of therapeutic agents of greater specific nature.

GENERAL CONSIDERATIONS

Before dealing with the different groups of drugs, it is necessary to review briefly the physio-pathology of blood and blood forming organs so that their pathogenesis and mode of drug action, can be properly understood.

- Blood Constituents:** (a) The volume of blood in an adult is about 5.5 litres, of which, the plasma represents 3.3 litres and the corpuscles 2.2 litres. The red marrow represents 3-5% of the body weight.
- (b) The life of a R.B.C. is about 120 days and about 10^{12} cells are formed daily in the marrow and about a tonne during the span of life of a man.
- (c) About 2-6 gm. of iron is present in the body, 60% of which circulates as haemoglobin. About 26 mg. is liberated from the breakdown of R.B.C./day and about 15-20 mg. is absorbed from the food/day. An infant, at birth, has from 200—300 mg. of iron.
- (d) Normal daily requirement of iron therefore is extremely insignificant. This however increases during menstruation, lactation and childhood.

Erythropoiesis: The formation of normal R.B.C. in the bone marrow involves two distinct phases:

- (a) Formation of normoblasts from megaloblasts, passing through the stage of the erythroblast.
- (b) Conversion of normoblast to red blood corpuscles, passing through the stage of the reticulocytes, which if abundantly present in the circulating blood, are suggestive of heavy demands for the R.B.C. formation. (*Plate XXIX: Fig. 77*).

Plate XXIX

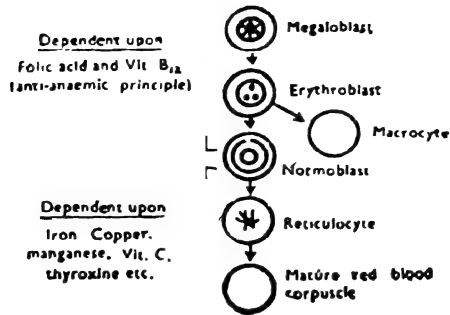


FIG. 77. Stages of development and maturation of red blood corpuscles

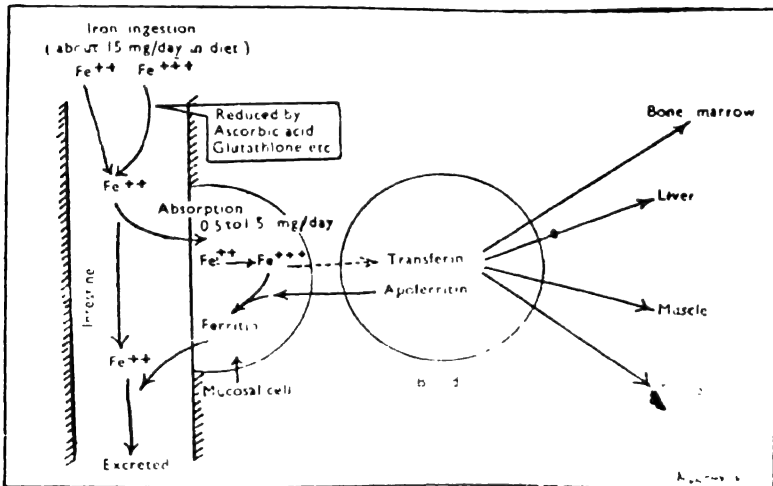


FIG. 78. Iron metabolism

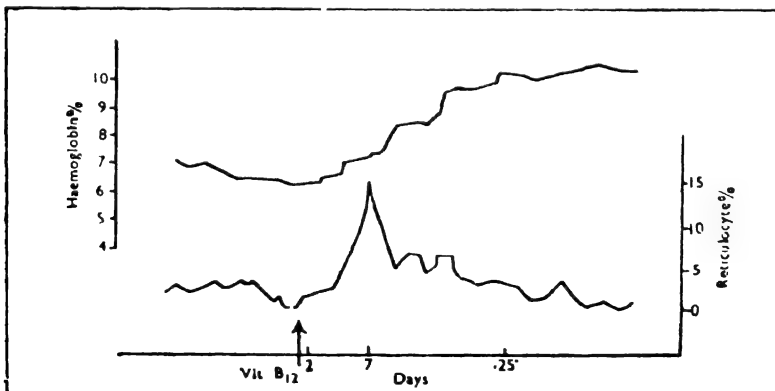


FIG. 79. Reticulocyte and haemoglobin responses in a patient of pernicious anaemia treated with Vitamin B₁₂ at (↑)

The role of the antianaemic principle (AAP) for the first phase and that of iron, copper, manganese, vitamin C, thyroxin and globulin for the second stage of erythropoiesis, is essential. In case of any deficiency of the A.A.P., the normal maturation process is disturbed and there is formation of macrocytes, which is a characteristic feature of pernicious anaemia and is associated with high colour index. It is consequently known as *macrocytic hyperchromic anaemia*.

In case of any deficiency of the latter group of substances, transformation of normoblasts to the final stage of erythrocyte, with adequate formation of haemoglobin, is disturbed and thus various types of abnormal cells—poikilocytes, anisocytes etc. are found in the circulating blood. This type of anaemia is known as *microcytic hypochromic anaemia*. The megloblasts contain normal or increased DNA and RNA. Thymidine is actively incorporated in the DNA and this can reverse megaloblastosis of folic acid deficiency but not of vitamin B₁₂. The conversion of megaloblast to normoblasts is not done by thymidine but by B₁₂. The megaloblasts then go into a state of unbalanced growth because of the impaired synthesis of deoxyribonucleotide, the precursor of DNA.

Haemoglobin Formation: It is a very complicated process, the understanding of which has been much facilitated by the introduction of isotopic studies in recent times. Haemoglobin is a conjugated protein of 67,000 mol. wt., containing iron pigment (0.34%) and globin, the former having 4 pyrole rings and is a metalloporphyrin. The divalent iron is bound in stable covalent linkage within the prophyrin ring of the *heme* with additional coordination position attached to the globin—peptide chains. The molecule of O₂ is bound reversibly by the iron of haemoglobin for transport throughout the body. Oxidation of iron to the ferric state, as in methaemoglobin, causes haemoglobin to lose its ability to carry oxygen. The haemoprotein of striated muscles, of mol. wt. of 16,500, is known as *myoglobin*. It has much greater affinity for O₂ than haemoglobin. As a component of all cells, iron is present in most of the enzymes: catalase, peroxidase, cytochromoxidase, reductase, succinic dehydrogenase, flavoproteins etc. It is now believed that haemoglobin is not synthesised in the red marrow but in the immature erythrocytes with the help of: (a) Iron (b) Pyrrol groups for porphyrin synthesis (c) Amino acids for globin synthesis.

After decades of intensive research, the structure of this complex respiratory pigment, has now been established by synthesis. (Plate XXX, Fig. 80).

Plate XXX HAEMATINIC PRINCIPLES. COAGULANTS, ANTICOAGULANTS

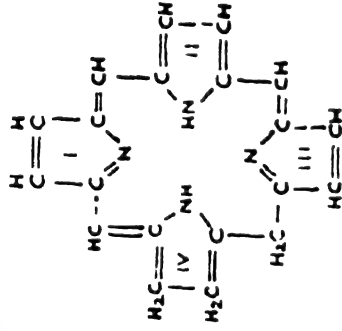


FIG. 80 (a) PYRROLE RING

FIG. 80 (b) PORPHYRIN

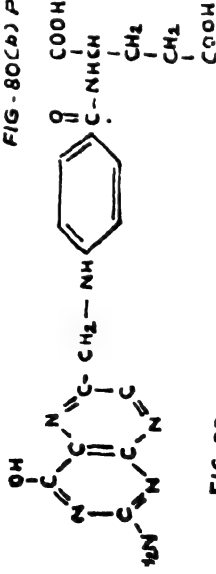


FIG. 82: FOLIC ACID

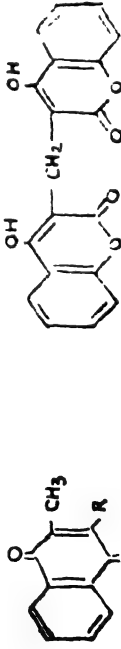


FIG. 84 DICOUMAROL

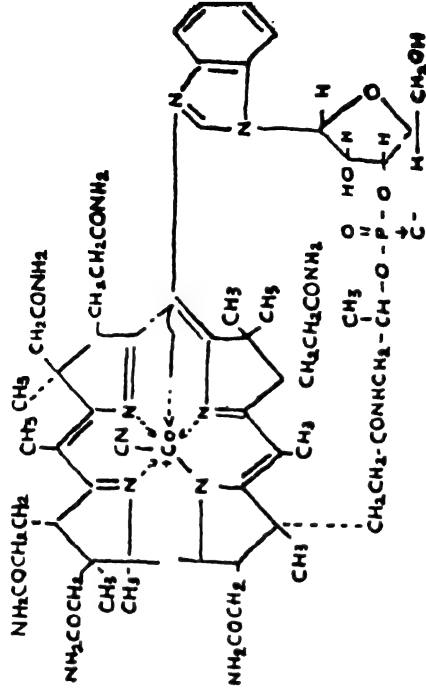


FIG. 81: CYANOCOBALAMINE

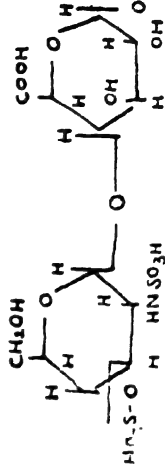


FIG. 85. HEPARIN

FIG. 83: VITAMIN K

Antianaemic Principle. Is formed by the interaction of the *extrinsic factor* supplied by the food stuff and the *intrinsic factor* elaborated by the fundus of the stomach. The former has now been definitely identified as *vitamin B₁₂* and not folic acid, which is inadequately present in the liver and aggravates neurological lesions of pernicious anaemia. The intrinsic factor is needed only for the absorption of A.A.P. through the G.I. tract for being stored in the liver. If *B₁₂* is given parenterally, the intrinsic factor becomes redundant. This is the 'revised hypothesis of Cassell'. As A.A.P. is stored in the liver, the extract is physiologically active in pernicious enaemia.

Leucopoiesis. The white blood corpuscles are very important cells and are of several types: (a) *Granular*—polymorphs, basophils and eosinophils (b) *Non-granular*—monocytes, lymphocytes.

Leucocytes: are produced in the bone marrow and lymph nodes from precursor cells and after successive stages of maturation, the fully developed forms are released in the blood. The various stages of leucopoiesis are:

Granulocytes: These are formed in the *bone marrow*. The primitive cell is converted to a big immature cell, called (i) *myeloblast*, which has scanty cytoplasm, coarse nucleus and no granules. The next are (ii) *premyelocyte*, (iii) *myelocyte* and (iv) *metamyelocyte*, which are more mature forms, in which, cytoplasmic granules start appearing. Metamyelocytes are converted to (v) *stab cell* and (vi) *mature granulocytes*, the last two forms being present in the peripheral blood.

Lymphocytes: are formed in the *lymph nodes* and their stages of formation are *lymphoblast* → large and small → *lymphocytes*. *Monocytes* are formed from the monoblaste in the reticuloendothelial system.

Regarding the genesis of these various types of formed elements in the blood, *two* different theories have been conceived. According to the *monophylactic theory*, all the blood cells are derived from a common *primitive cell*, the *haemocytoblast* or *stem cell*, while according to the *polyphylactic concept*, for every variety of blood cells, there is a distinct type of blast cell viz. erythroblast, myeloblast, lymphoblast and monoblast. Though the latter view may be understandable, the first would appear to be sounder, from the standpoint of genetic evolution.

Clinical significance. The leucocytes in the blood can increase during acute and chronic bacterial infections, so much so, that an increase in the count of a specific type of cell can lead to a rough identification

of the type of infection, e.g. polymorphs in the acute suppurative processes and lymphocytes in chronic diseases like T.B. The leucocyte count may fall in diseases like typhoid and malaria or if the bone marrow and the reticuloendothelial system are poisoned by cytotoxic drugs. In both these categories of disorders, the mature elements are altered. However, in leukaemia, which is a proliferative disorder of the leucopoietic tissues, there is excessively rapid formation of leucocyte precursors, with the result that immature leucocytes are poured into the blood. Those leukaemias in which more primitive cells like blasts are more common, are called *acute leukaemias* and their outlook is very grave.

In *chronic leukaemia*, the more mature forms of cells like myelocyte are found in abundance. This condition can be palliated by certain newly derived drugs and the life of the patient can be prolonged. Both these conditions will be dealt with in the chapter of antileukaemic and antimalignancy drugs.

Coagulation. It is an inherent property of blood not to coagulate intravascularly but to do so when any bleeding occurs. A large number of factors, about 13 of them, are implicated in the coagulation of blood, which, as per original concept of Morawitz, occurs in 3 distinct stages—(a) Formation of *active prothrombin*, (b) Conversion of prothrombin by thromboplastin to *thrombin* and (c) Finally, conversion of fibrinogen by thrombin to *fibrin*, which forms the matrix of the clot.

For the initiation of the above phased reactions, the starting material is *thromboplastin* which is derived as *intrinsic* or blood thromboplastin by the interaction of Christmas factor IX, Ca^{++} , antihæmophilic globin factor VIII, and platelet disintegration—Factors V & X and as *Extrinsic tissue* thromboplastin from tissue damage—Factor V, VII, X and also Ca^{++} . Both of them together subscribe to the conversion of prothrombin to thrombin, which, acting on fibrinogen, convert it to fibrin, leading to the coagulation of blood. The clot thus formed, is resolved by fibrinolysin, along with the enzyme streptokinase.

Antithrombins. These are formed in blood during anticoagulant therapy and interfere with the ability of thrombin to catalyse the formation of fibrin. They are proteinases in nature and are capable of either inactivating or completely removing thrombin from the coagulation mechanism. Their presence in *active* and *inactive* forms, has been described.

With this general background, we may now go through some of the specified blood conditions and their drug therapy, listed for study, in this chapter.

DRUGS ACTING IN ANAEMIAS

These drugs, conventionally known as *haematinics*, help in the regeneration of blood, improve haemoglobin concentration of R.B.C. and correct cellular abnormalities by reinstating normoblastic reactions. As their study presupposes an understanding of different types of anaemia and their underlying pathogenesis, it is necessary to outline this first, before dealing with the drugs indicated in this therapy.

CLASSIFICATION OF ANAEMIAS

	From deficiency of Hb forming factors.	<i>Primary</i> : Chlorosis of young women, <i>Secondary</i> — nutritional anaemia of infants.
Microcytic hypochromic.	Due to loss of R.B.C.	From haemorrhages or from haemolysis as in malaria, kalazar.
Macrocytic hyperchromic.	Due to deficiency of anti-anaemic principle.	<i>Primary</i> : pernicious, Addisonian type; <i>Secondary</i> : sprue, pregnancy, worms.
Aplastic.	From depression of bone marrow function.	Deep X-ray and radium therapy, drug allergy, heavy metals.

ALTERNATIVELY

I. *Dyshaemopoietic*: from deficiencies of:

- (a) Vitamin B₁₂ — Addisonian and gastrectomy macrocytic type
- (b) Folic acid — Sprue and nutritional megaloblastic anaemia.
- (c) Iron — Chlorosis, pregnancy, dietary deficiency and hypochromic anaemias in subthyroid states.
- (d) Achrestic anaemia. No deficiency but diminished uptake of iron by bone-marrow.

II. *Haemorrhagic anaemia*:III. *Haemolytic*

- anaemia*: — *Congenital*: spherocytic, cooley's sickle cell anaemia.
- *Acquired*: malaria, blood transfusion, snake bite.

IV. *Aplastic anaemia*: *Primary* or idiopathic.
Secondary—radiation, cytotoxic and other drugs.

HAEMATINICS

The drugs which help in the regeneration of blood, improve haemoglobin percentage, R.B.C. count and correct cell abnormalities, are known as *haematinics*.

CLASSIFICATION

Drugs acting on microcytic hypochromic anaemia.	(a) Major drug — iron.
	(b) Minor drugs — Cu, Mn, cobalt, thyroxine, Vit. C.
Drugs acting on macrocytic hyperchromic anaemia.	(a) Major drugs — Vitamin B ₁₂ , folic acid & liver.
	(b) Minor drugs — Stomach, HCl dil.

MICROCYTIC ANAEMIA

Of the drugs listed above for microcytic hypochromic anaemia, the *minor group* of thyroid, vitamin C and cobalt will only be very briefly reviewed and the *major drug*—iron, the sheet anchor of iron deficiency anaemia along with copper and manganese, will be studied in greater details.

Thyroid. It increases oxygen need of tissues resulting in increased marrow response. It is indicated mostly in thyroid deficiency anaemias. *Vitamin C* — possesses no special action on any particular stage of the maturation of R.B.C. It is indicated in hypo-vitaminosis C anaemias and as a general stimulant of the bone marrow.

Cobalt. It has a definite hæmopoietic effect in animals. It acts on tissue respiration and is present in vitamin B₁₂. It seldom produces any deficiency in human beings.

IRON

An old pharmacological agent, long used in the Ayurvedic medicine as 'lauha bhashma' or roasted iron, macerated in oil. The metal derives its name from the Greek God of War—'Mars' and is a symbol of strength. Sydenham used to 'comfort the languid, worn out blood, and give a spur to the sunken with iron. Blaud and his nephew had made fortunes with their pill, still known as *Blaud's pill*. In spite of all advances, so far made, iron still holds its unique position in 'iron deficiency anaemias', unsurpassed by any.

Iron is available in *two forms*: *Inorganic*:—ionisable, astringent, giving customary reactions of iron. Most of the important preparations are available from this form. *Organic*: nondisseciable, customary reactions of iron are negative and very little used in therapeutics. Cytochrome, haemoglobin and food irons are present in this form.

Preparations. Numerous and can be grouped as:—(a) *Reduced iron* or *ferrum reductum*—an iron oxide. (b) *Ferrous salt*. (c) *Ferric salt* (d) *Scale preparation* and (e) *Miscellaneous organic preparations*.

I.	INSOLUBLE	Ferrum reductum	60—600 mg.
		Pil ferri carb. (Blaud's pill)	300—1800 mg.
II.	SOLUBLE	Ferrous salts.	
		Ferri sulphas.	60—300 mg.
		Pil aloes et ferri.	240—480 mg.
		Easton's syrup.	1800—3600 mg.
		Ferric salts.	
		Liq. ferri perchlor.	300—900 mg.
		Injecti. ferri.	900—1800 mg.
		Scale preparations.	
		Ferri et ammon. citras.	1200—2400 mg.
		Ferri et quin. citras.	300—900 mg.
III.	Miscellaneous.	Sacchared iron oxide—uniferon, Imferon, ferrivenin.	50—200 mg.

Reduced iron: greyish black powder available in tablet or capsule forms. Due to undependable absorption, its use has been discarded.

Ferric salts: astringent, irritant and not used internally.

Ferrous salts: *Ferrous SO₄*. Bluish green prisms, soluble and mostly used. Ferrous carbonate is insoluble and is much less absorbed.

Scale preparations: Soluble ferric salts, dark red, light, translucent scales, less astringent and can be given orally or by injection.

PERCENTAGE UTILISATION

Preparations	Fe content of average dose	Percentage utilisation
Ferrous chloride	200 mg.	25
Ferrous sulphate	180 mg.	14
Blaud's pill	400 mg.	8
Ferri et ammonium citras	1600 mg.	3

It is evident that blaud's pill and scale preparations are very little utilised in the body. Though the iron utilisation of ferrous chloride is more than that of ferrous sulphate, the latter is less irritant and more

used. Further, because of the astringent and irritant actions of iron preparations, high doses are to be deprecated.

Standardisation. Any preparation increasing 1% haemoglobin per day, is considered to be a standard one. This is effected by 25 mg. of iron utilised. As only 15-20% of prescribed iron is absorbed, FeSO_4 —200 mg /day may usually suffice the need of the patient.

Metabolism. (Plate XXIX; Fig. 78). This is extremely complex, because of (a) variable absorption of iron in normal and anaemic persons, (b) inadequate excretion of parenteral iron and also (c) risk of haemosiderosis.

DISTRIBUTION

<i>Circulating iron</i>	<i>Available iron reserves</i>	<i>Nonavailable iron reserves</i>
Blood haemoglobin 57%	Liver, spleen, bone marrow 20%	Myohaemoglobin: 7% Parenchyma iron cytochrome & catalase 16% iron.
Total 57%	20%	23%

In whatever form administered, a number of factors regulate the absorption, utilisation and excretion of iron.

1. Iron is converted to ferrous form in the stomach by hydrochloric acid, ascorbic acids, cystine and SH containing proteins. This is hindered by phytic acid and phosphates.

2. In duodenum and upper jejunum, iron is absorbed by mucosal epithelium after following biochemical changes.

- Ferrous ion is converted to ferric state by enzymatic action of oxidation.
- Apoferitin, a colourless protein in mucosal cells, combines with ferric ions forming ferritins.
- This is reduced to ferrous form by the *redox mechanism* of cells, for diffusion into capillaries.
- This goes on till the cells are completely saturated and there is equilibrium with plasma ferric ions, after which, there is no further absorption. This is known as *mucosal block*.

3. In blood, in the presence of CO_2 , iron is oxidised to ferric form again. It then combines with a globulin forming transferrin, in which form, it is carried to the tissues and stored as *ferritin*.

4. After transport, iron is utilised for (a) haemoglobin synthesis, (b) cellular oxidation by cytochrome and other respiratory enzymes and (c) storage and excretion as referred above. Any haemorrhage is the cause of greatest iron loss.

Radioactive Iron. This is prepared by the bombardment of neutrons, which along with protons, constitute the nucleus. Thus transmutation with changing of atomic weight and development of radioactivity, occurs which can be detected by a 'Geiger-Muller Counter' and iron metabolism in different parts of the body studied. The natural atomic weight of iron is 55.9 and this is changed to 59. This unstable compound temporarily acquires radioactivity with radiation of B-rays and has a *half life* of 47 days.

From this study, the following facts have been revealed:

(a) Iron absorption is 70 times greater in anaemia and this occurs in 4-8 hours from the intestine. (b) Radioactive iron appears in the R.B.C. in 4 hours and in haemoglobin in 24 hours. It is completely converted to haemoglobin in 4-7 days. A trace of copper and manganese hastens haemoglobin formation. (c) Radio active iron is distributed as R.B.C., plasma, muscle haemoglobin and visceral irons. It is stored in the nuclei of cells, bone marrow, spleen and liver. (d) It is excreted in gut to the extent of 10-20 mg., in urine, 0.5 mg/day and a little in the sweat also. The part of iron excreted in bile, is partly reabsorbed. The unabsorbed portion in the gut makes the stool dark, due to the formation of sulphides and phosphates. Iron loss in menstrual blood is about 10-40 mg/month.

Parenteral Iron. Heath et al (1932), observed that ferric ammonium citrate—32 mg. I.M. was equivalent to 1000 mg/os. Since then, ferrous adenylate, ferrous ascorbate etc. were brought into use but were found to be toxic.

Nissin and Robson (1949) introduced the new compound of 'saccharated iron oxide' for I.V. injection. This was prepared by the interaction of ferrous oxide and sucrose in presence of sodium hydroxide. The L.D.₅₀ of this preparation was, found to be 300 mg/kg. weight of mice.

This dose given I.V., produced no toxic effect in man and it is now extensively used in gradually increasing doses of 25 mg. to 200 mg. in one or two injections, daily. It is 100% utilised in haemoglobin formation and increases haemoglobin by 2% per day. The preparation is very useful in oral iron refractory cases and also in severe forms of anaemia with low E.S.R.

Actions. (a) *Externally:* Liq. ferri perchlor is an astringent and styptic.

(b) *Internally:* There is staining of the oral cavity due to formation of iron tannate and sulphide. There is irritation of stomach and intestine and on prolonged use, indigestion and constipation.

(c) As a constituent of respiratory enzyme-cytochrome, it plays an important part in tissue respiration and as a constituent of haemoglobin.

Incompatibilities: Almost with everything and particularly tannic acid containing substances. Quassia and chirata, do not contain any tannin. It is better to prescribe iron preparation alone.

Uses. Many are the unsubstantiated, conventional uses of iron. It acts only in specific iron deficiency conditions.

(a) *Externally:* Haemostatic and anti-inflammatory paints and gargles.

(b) *Internally:*

(i) Anaemic and subanaemic states—hypochromic type, after haemorrhages and malaria.

(ii) Neurological complications of pernicious anaemia, if the colour index is below normal.

(iii) Amenorrhoea—Pilula aloes et ferri.

(iv) Lastly, Easton's syrup, Syrup ferri hypophos and ferrous iodide, are sometimes used as general tonic in anaemia and nervous debility states.

Special points. (a) Iron is not a panacea and should be used only when indicated. Any prolonged therapy may lead to the G.I. irritation and constipation.

(b) A good preparation is to be chosen on the basis of iron utilisation and tolerance, given after meals and changed from time to time. It should be swallowed and in cases of headache and indigestion, suspended.

(c) Intravenous iron may give vomiting, pallor and fall of B.P. It should better be given slowly and I.M. injections should be preferred.

COPPER

It is universally distributed in water, soil, living tissues, nuts, cereals, fish and milk. The daily requirement is about 6 mg. and the major part is present in the R.B.C. and liver. Its rate of excretion is about 0.1 mg/litre of urine.

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Preparations. (a) Cupri sulphas (blue vitreol): 15-120 mg; *Emetic dose*: 300-600 mg. (b) Ung. Cupri oleatus—B.P.C. antiseptic and parasiticide.

Role in Haemopoiesis. *Growing rats* kept on milk alone, produce nutritional anaemia and do not improve after administration of purified iron preparations. When copper and iron are added to the milk, they show marked improvement. Copper thus may be helpful in the utilisation of iron for haemoglobin formation but it does not seem to stimulate blood formation.

Uses. *Externally:* (a) Copper sulphate sticks are applied locally for destroying the granulation tissues in trachoma and a 2% lotion is used for chronic indolent ulcers and ung. cupri is used in ring worms. (b) Copper sulphate 2×10^{-5} has been used for destroying snails, the vectors of *Schistosoma haematobium* of bilharziasis.

Internally: (a) Nutritional hypochromic anaemia of infants. (b) Phosphorus poisoning—180 mg./60 ml. every few minutes till vomiting and then followed by a saline purgative. It tends to form CuPO_4 , which is less toxic.

MANGANESE

It is widely distributed in plants and animal tissues. The deficiency causes: (a) retarded growth, (b) low testicular function and (c) defective bone formation in experimental animals.

Preparations: *Fersolate tablet*, containing FeSO_4 : 60 mg., Cu. and MnSO_4 : 0.6 mg. each. 2-3 tabs with HCl dil: 1 ml and blood transfusion, have been considered to be a good line of treatment in acute hypochromic anaemia. On prolonged use, manganese however, may cause parkinsonism and cirrhosis of liver.

MACROCYTIC ANAEMIA

Of the drugs listed for macrocytic, hyperchromic anaemias, though Vitamin B_{12} has taken away the place of most of the other drugs, *three* of the other members—liver, stomach, folic acid, will also be studied, in the sequences of their discovery, along with Vit. B_{12} .

LIVER EXTRACT

This to start with, was an important landmark in the therapy of pernicious anaemia and will be dealt with in some detail.

The extract is a selected fraction, obtained from cattle liver, with alcohol and glycerine, containing the specific A.A.P.

Chemical Nature. (a) The active principle is water soluble, thermostable at pH₆, resistant to proteolytic enzymes and hydrochloric acid. (b) It is a peptide containing C.H.N.O₂ and P with a molecular weight of 10,000. It does not contain any thiamine or riboflavin. (c) It possibly contains more than one chemical entity, as too much purification, removes a part of its overall activity.

Preparations. *Oral:* (a) Whole liver: 250-500 gm/day, (b) Dry liver extract: 12.5-25 gm. (c) *Liq.* Liver extract: 6-8 t.s.f./day.

Parenteral: Campolon, anahaemin, neohepatex, hepastab I.M. or I.V., differing in their degree of purification, local reactions, unitage and potency. *Dose:* 1-5 ml. containing 15 units/ml approximately. Initially, 1 ml thrice a week and gradually reduced as the blood picture improves. 3 to 4 times bigger doses are to be prescribed in subacute combined degeneration.

Actions. (a) The A.A.P. acting on the marrow, reinstates the normal function by replacement, in the following sequence: (i) removal of megaloblasts, (ii) normoblastic reaction and (iii) formation of reticulocytes and normal R.B.C.

(b) All the signs and symptoms of P.A.—hyperchromia, shortness of breath, pain, icterus, oedema, beef tongue, diarrhoea, megaloblastic hyperplasia of the marrow, leucopenia and thrombocytopenia, disappear but the achlorhydria does not improve.

(c) Neurological complications: peripheral neuritis and subacute combined degeneration—may not improve but their further progress is checked.

(d) The action is fairly rapid and reticulocyte response occurs in 2-5 days, attaining the peak in 8-10 days. The increase in R.B.C. count occurs at a rate of 0.5 million/week, approximately and the blood picture returns to normal in 2-4 months.

Standardisation. (a) This is clinical and not experimental. Untreated patients with low R.B.C. count (0.5-1 million/ml) are selected and the potency of the drug determined from the % of reticulocytic responses, shown below and in *Plate XXIX; Fig. 79.*

<i>Initial R.B.C. in million/cubic millimeter</i>	<i>Maximum reticulocyte response %</i>
1.0	41
1.5	28
2.0	18
2.5	11
3.0	5

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By this test, it has been observed that fresh liver—250 mg is equivalent to 12.5 gm of the dry extract. Purified preparations are about 30 times more active than the oral ones.

Accidents. (a) *Local:* pain and induration, which are protein reactions.
(b) *General:* acute B.P. fall and allergic manifestations, with urticaria, erythema, dyspnoea and even collapse.

Uses. (1) Before the discovery of Vitamin B₁₂, they were numerous—
(a) P.A. (b) Other macrocytic anaemias—tropical, anaemias associated with tape worm, pregnancy and gastric carcinoma. These uses have been given up in favour of Vitamin B₁₂, now.

(2) In atrophic gastritis associated with P.A., stomach preparation with HCl dil. and in cord lesions, liver, along with iron, have been used but now vitamin B₁₂ is preferred, in all these cases.

STOMACH

Hog stomach defatted with benzene and dried to powder form. Powder: 7.5—30 gm. is equivalent to 60—240 gm. of fresh stomach.

Preparations. (a) *Ventriculin:* 'P.D.' (desiccated powder): 20-30 gm/os/day, initially and a maintenance dose of 10 gm/day, thereafter.

(b) *Pepsac, exstomak:* 10·gm. t.i.d. along with liver.

(c) *Extrallen:* a liver-stomach concentrate. *Dose:* 6 gm/day.

The stomach preparations supply the intrinsic factor and may act as complementary to liver treatment. They have disagreeable taste and when prescribed they have to be mixed with fruit juice and milk for masking the taste. In actual practice, it is very seldom used these days, anymore.

FOLIC ACID

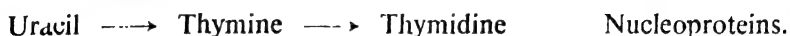
Also known as P.G.A. or pteroyl glutamic acid—the lacto vacillus factor, it was isolated by Snell in 1941 from spinach leaves and therefore the name of 'folic acid' was assigned to it. It is present in liver, yeast, kidneys and also mushrooms. It was synthesised: 1945.

Chemistry. Folic acid has a complicated structure with 3 distinct groups of (a) glutamic acid, (b) p-amino benzoic acid and (c) a pteridyl ring, as shown in Plate XXX: Fig. 82.

It is an orange-yellow powder and insoluble in water. In the food, it is present in the form of 'conjugates' from which it is released in

intestine by the bacterial flora. This is affected by sulphonamides. In pernicious anaemias, the conjugate is not degraded in the intestine and therefore P.G.A. is not available for absorption.

Actions. An important coenzyme involved in erythro and granulopoiesis tissue growth and metabolism. These actions are mediated through nucleoprotein metabolism, as under



The PABA moiety of folic acid is the growth factor for *Lactobacillus casei*. Its concentration in malignant tissues is high and therefore 'antifolic acid' compounds are used in leukaemias. It has no action on the neurological lesions of P.A. On the contrary, it may precipitate these lesions when given alone in P.A. by causing an acute deficiency of Vitamin B₁₂ and R.N.A.

Uses. Rather limited—(a) Macrocytic anaemias other than PA—sprue, anaemia of pregnancy, nutritional anaemia, referred early and also (b) Aggranulocytosis. *Dose:* 10-20 mg/os I.M., I.V.

Folinic Acid. (Citrovorum factor) is an active metabolite, formed in the body, by the reduction of folic acid, in the presence of ascorbic acid. It is 500 times more potent than the parent substance, but is not used in therapeutics, as yet.

CYANOCOBALAMIN (VITAMIN B₁₂)

Since the introduction of liver therapy in 1929 by Murphy and Minot, much work has been done on the identification of A.A.P. which is now believed to be Vitamin B₁₂. It was isolated from liver concentrates in 1949 by Ricks and Lester-Smith, independently, as crystalline red pigment, about 1000 times more potent than liver. This was designated as vitamin B₁₂ and 1 µg of this, was found to be equivalent to 1 U.S.P. unit of liver.

Chemistry and Source: Vitamin B₁₂, a member of the B complex, is a 5:6 dimethyl benzimidazole derivative, containing 4.5% of cobalt. Its molecular weight is 1,300 and there are at least 4 variants of cyanocobalamin. It also contains glutamic acid and 3 atoms of phosphorus (Plate XXX: Fig. 81). It is commercially obtained from *Streptomyces griseus* and can be assayed microbiologically on '*Lactobacillus leishmanii*'.

Metabolism. (a) About 70% of vitamin B₁₂ is absorbed from the intestine in the presence of the intrinsic factor but in P.A. this is restricted to 10% only.

(b) It is present in blood in free and bound forms, the plasma concentration being 400 µg/ml. In P.A. the plasma concentration is only 1/10th of the normal.

(c) It is distributed in all the organs and stored maximally in liver, kidneys and spleen. It is excreted in urine gradually.

Actions. (a) Cyanocobalamin is the most potent agent for reversing all haematological and neurological abnormalities of P.A. Even 10 µg. may produce dramatic effect. Reticulocyte response is produced in 2-3 days, with a peak response of 60-70% in a week. The R.B.C. count, haemoglobin % and leucopenia markedly improve and the patient becomes normal in 1-2 months.

(b) It possesses neurotropic and lipotropic actions and helps in the synthesis of neuroproteins, prevents fatty infiltration of liver and is thus useful in pernicious anaemia with neurological complications, neuritis and also in cirrhosis of liver.

Mechanism of Action. (a) B₁₂ catalyses the synthesis of nucleosides from purines and pyrimidines, which go into the formation of blood cells or nerves.

(b) It helps in the genesis and transfer of methyl groups and thus acts as a lipotropic agent.

Comparison. All the three drugs are endowed with potent haemopoietic actions in P.A., though there is some difference of opinion about their exact mechanism of action.

Liver Extract: Though formerly believed to contain A.A.P., it is now believed to act by virtue of its B₁₂ and folic acid contents. It is 1/1000 as potent as B₁₂, gives protein reaction, cannot be duly standardised and is less effective in subacute combined degeneration, due to inadequate B₁₂ and folic acid contents, in it.

Folic acid: A good erythropoietic agent but less efficacious than B₁₂ and aggravates cord lesions by setting up the chain reaction in ribonucleic acid synthesis, in which, the meagre store of vit. B₁₂ in P.A., is further used up and its acute deficiency precipitated. It is therefore contraindicated in pernicious anaemia.

Vitamin B₁₂: It is now the accepted antianaemic principle and is the most potent, easily purified and standardised and can correct all abnormalities of P.A. It needs a small quantity of folic acid for the conversion of uracil into thymine referred above, for nucleo-protein synthesis. Besides the above, B₁₂ is also concerned with the neogenesis of methyl group for transmethylation and incorporation of amino acids in the proteins of nerves and also maintenance of thiol (-SH) groups in a reduced state. All these subscribe to its beneficial action in P.A. and its neurological complications—subacute combined degeneration, for which, it is the drug of choice, at an adequate dose level.

Use. (a) Addisonian Pernicious anaemia—major use.

(b) Other megaloblastic anaemia, if the bone marrow is also involved.

(c) Anaemia of infancy and pregnancy—respond better to folic and folinic acids and crude liver extracts.

(d) In sprue, also, it is effective but needs folic acid in addition.

(e) Miscellaneous—Cirrhosis of liver, viral hepatitis and pellagra.

(f) In other neurological disorders also, it is sometimes used but further confirmation needed.

THERAPEUTIC CONSIDERATIONS

Iron Deficiency Anaemias. Whatever might be the underlying cause, the onset is often insidious and the patient complains of weakness, soreness of tongue, numbness and tingling, pallor, giddiness, cheilosis, flatulence, dysphagia, palpitation, dyspnoea and neuralgic pains. The management comprises:

(a) Rest in bed if haemoglobin is below 40%.

(b) Correction of aetiological factors—menorrhagia, ankylostoma infection, etc.

(c) Iron therapy—(i) oral (ii) parenteral, indicated in the text. Ferrous sulphate, iron dextran complex, fersolate tablets, are satisfactory.

(d) Small blood transfusions, adequate proteins, proteolysed liver, ascorbic acid and also folic acid in small doses, may be used.

(e) Relief of glossitis, dysphagia, anorexia, constipation and neurological symptoms by appropriate uses of vitamins including B₁, dilute HCl, pepsin and laxatives, may be needed. Overall results of suitable treatment is satisfactory.

Pernicious Anaemia. Like insulin in diabetes mellitus, it is a replacement therapy, requiring careful management of acute conditions and continued follow up, almost throughout the whole life. The treatment aims at: (a) restoring the blood picture to the normal. (b) relieving signs and symptoms, and (c) preventing the occurrence of neurological lesions.

Vitamin B₁₂ therapy: is now the only accepted treatment in P.A. and with diluted HCl, proper diet and small transfusions, it is considered to be good enough for meeting with all the exigencies of the disease. An *initial loading dose* of 100-500 $\mu\text{g.}$, I.M., followed by 50-100/ $\mu\text{g/week}$, till the blood picture is normal, followed by a maintenance dose of 50/ $\mu\text{g/month}$ for the rest of the life, is prescribed. In cases of neurological lesions, increased initial loading dose of 500/ $\mu\text{g/day}$ for two weeks is advisable. With this type of therapy, the prognosis of this fatal disease has now been completely modified, changing the erstwhile fatality rate of 96% to the cure rate of 95%, thus changing 'bottle of despair to the wine of hope', as aptly expressed by Krantz.

Shot Gun Therapy. It is a polypharmacy, using haematinics of both the groups in any case of anaemia. It is an expression of wavering clinical confidence about (i) Correct diagnosis (ii) efficacy of prescribed drugs and (iii) skill in the assessment of result. This often leads to (i) inadequate dosage of the correct drug (ii) difficulty in the assessment of results and (iii) masking of neurological lesions. This procedure is strongly deprecated.

DRUGS ACTING ON OTHER BLOOD DISORDERS

Besides anaemia, just studied and leukaemia dealt with in Chapter 50, there are two other conditions—(a) polycythaemia and (b) agranulocytosis, due to hyper and hypoblastic reactions of R.B.C. and W.B.C. respectively. The pharmacological responses to these conditions are:

1. *Polycythaemia Vera*—Phenyl hydrazine, Radio Phosphorus.
2. *Agranulocytosis*—Folic acid, Pentnucleotide.

The importance of both these conditions is considerable, inasmuch as, the first is difficultly amenable to treatment and the incidence of the second, because of newer drugs, is becoming increasingly greater.

PHENYL HYDRAZINE

Buff coloured, oily liquid, the hydrochloride salt is soluble in water. The solution darkens on exposure. It is therefore used in capsules,

containing 50 mg. in each. It is absorbed through the G.I. tract and excreted slowly in urine, which also darkens on exposure. It is a cumulative poison. The drug causes marked depression of the R.B.C. with splitting of haemoglobin into haemin and denatured globin, formation of methaemoglobin, inducing fragility of R.B.C. and haemolytic crisis.

In a dose of 50 mg. cap/os/daily, for the first few days, followed by 50 mg/week, the drug has been made use of, in polycythaemia vera, with good results in about 50% of cases, but because of its toxicity, its use has now virtually been relegated to the newly discovered P_{32} , which is less toxic, and more efficacious than the former. The *toxic manifestations* comprise—(a) gastric disorder, (b) jaundice, (c) dermatitis and even (d) aplastic anaemia. Its acetyl derivative—*Acetyl phenyl hydrazine*, is relatively less toxic but yet, not as much used as radiophosphorus.

RADIO-ACTIVE PHOSPHORUS (P_{32})

Normally the nucleus of phosphorus has 15 protons and 16 neutrons and an atomic weight of 31. When it is bombarded with high speed particles of deuteron, P_{32} is formed, having a half-life of 14 days. It is then made into a sodium salt for medicinal use. The uptake of radiophosphorus depends on the rate of phosphorus metabolism, as well as, cellular proliferation. It is concentrated in bone marrow, liver, brain and neoplastic tissues, which are then subjected to the beta rays radiation. *Dose*: orally 3-5 mc. and I.V. 2-4 mc in 20 ml of solution, initially and repeated after 4 months.

Uses. (a) Polycythaemia. (b) Chronic myeloid and lymphatic leukaemia. (c) Acute plasma cell leukaemia.

Management of Polycythaemia Vera. or *Maladie de Vaquez*. This is a very serious condition, in which, there is a considerable stimulation of R.B.C. count going up to 8-14 million/ml, haemoglobin content rising to 18-24 gm, viscosity of blood rising to 5-8 times, and total blood volume twice the normal. There is also cyanosis, thrombosis and splenomegaly, the condition usually having a fatal termination.

The *therapeutic measures* comprise — (a) Repeated venesection for removal of excess blood volume load.

(b) Induction of haemolysis by acetylphenyl hydrazine: 30 mg. t.d.s. for 7-10 days, followed by a rest period.

(c) Depression of the bone marrow by irradiation or by *radio phosphorus*: 3-8 millicuries I.V. initially, followed by 1-5 milli-

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curies every 3-6 months, as long as the red cell count remains not more than 6 million per cu. mm.

PENTNUCLEOTIDE

Nucleic acid and its hydrolytic products, nucleotide, xanthine, guanine and adenylic acid are believed to act as natural stimulants for the formation of granulocytes in the body.

Pentosenucleotide, a derivative of nucleic acid, is obtained from yeast and is available in the form of 10 ml. containing 0.7 gm. of the drug. It has been in use in agranulocytosis for a fairly long time.

Actions. Nothing much of real importance excepting mild bradycardia, fall of B.P. and inhibition of plain muscles. It has however a stimulant action on the precursors of W.B.C. in the marrow and this has been the basis for its use in granulocytopenia, consequent to a disease or drug therapy. It may sometimes give mild protein reaction of histamine type and also precordial distress.

Uses. *Agranulocytosis*, either idiopathic or due to drug allergy:—sulphonamide, arsenicals, amidopyrine, gold etc. with fever, sore throat, debility and extreme degree of susceptibility to infection, due to accompanying leucopenia.

For this condition, accepted therapeutic measures comprise:

- (a) Protective penicillin antibiotic therapy for averting the infection, as a substitute for granulocytes.
- (b) Specific stimulus for granulocyte formation by—(i) *pentnucleotide* twice a day I.M. for a week and then once a day, for another week, till the blood picture becomes normal again. (ii) *pyridoxine*, *folic acid* and also vitamin B complex. With early diagnosis and close supervision, the result is fairly satisfactory and the mortality rate has been reduced from 78% to almost nil.

DRUGS ACTING ON COAGULATION

They comprise *two* important groups: (a) Coagulants and (b) Anti-coagulants.

COAGULANTS

These represent a group of drugs—chemicals and thromboplastic agents, which are used as haemostatics in cases of bleeding. Though

their efficacies are unequal, they find ready uses in cases of haemorrhages.

Whole Blood. It not only makes up the volume deficiency but also supplies ready made constituents, responsible for the coagulation of blood. It is usually given in the form of transfusions after determining grouping and compatibility between the recipient and the donor.

Serum. Ordinary or hemopoietic in varying doses of 5-10 ml. I.M.

Coagulen. A blood platelet preparation which supplies prothrombin and thrombokinase. *Dose:* 5-10 ml. I.M.

Thromboplastin. A brain preparation which can be given orally or parenterally.

Stypven. A russell viper venom preparation containing thrombin. It is used *locally* in 1 in 10,000 concentration and in 1 ml. dose, *parenterally*.

Vitamin K. It helps in prothrombin formation in the liver. *Dose:* 5 mg. I.M. (Plate XXX Fig, 83)

Calcium. Any of the suitable preparations—chloride, gluconate or lactate, given orally, I.M. or I.V.

In addition to the above, a number of *new haemostatics* have been brought into use, in recent years, which are efficacious in stopping haemorrhages, on local applications.

Absorbable Gelatin Sponge. This applied *locally*, frequently moistened with thrombin solution controls capillary bleeding and is absorbed in 4-6 weeks. The contact does not give any untoward cellular reaction.

Gelfoam. It is a special brand of the above preparation available in sterile sections of 20 × 20 mm. and 80 × 125 mm.

Fibrin Foam. It is a dry sterile preparation of fibrin obtained from human plasma and acts as a mechanical coagulant. In combination with thrombin, it produces a mechanical matrix for the coagulation process. The foam mixed with thrombin and isotonic saline, is used in brain, kidney and liver surgery, when other methods of haemostasis are ineffective.

Oxidised Cellulose (Hemo-Pak, oxycel). This is a type of absorbable gauze or cotton. It is a very potent haemostatic and helps in the formation of artificial clot, due to the presence of cellulosic acid. It can be used in surgery where ligation is difficult. It is not usually meant for surface dressing, as it inhibits epithelialisation.

Thrombin. A sterile protein, prepared from mammalian prothrombin through the interaction of thromboplastin and calcium. Its potency is expressed as units of clotting activity: 1000-2000 units. It controls capillary bleeding during surgical interventions.

ANTICOAGULANTS

The problem of coagulation of blood has a far reaching importance in the management of a number of conditions, from the standpoint of therapeutics, as well as, prevention of complications.

Though a number of drugs are capable of retarding coagulation, only a few of them find their therapeutic applications through any of the following mechanisms:

- (a) Oxalates, citrates and fluorides. They act by the process of decalcification of blood.
- (b) Peptone solution. It is alleged to stimulate heparin formation and increase platelet resistance to agglutination.
- (c) Chicago blue and suramin. They increase the coagulation time.
- (d) Cobravenom. It may act as a thrombokinas and thus delays the coagulation of blood.
- (e) Hirudin obtained from the secretions of buccal glands of leeches, activates thrombokinas and increases the coagulation time.

The important anticoagulants belong to the following two groups:

- (a) *Heparin* and allied compounds.
- (b) *Dicoumarol*, tromexan, hirudin, depaxin, marcoumar and warfarin.

Alternatively, depending upon the duration of action, they can be classified as:

- (i) *Long Acting* — Dicoumarol, cumopyran.
- (ii) *Short Acting* — Heparin, tromexan, etc.

HEPARIN

Source. Heparin is secreted by the mast cells of liver, lungs and blood vessels. It was first isolated and purified by Howell (1928) from the liver.

Chemistry. It is mucoitin polysulphuric acid with hexosamine and hexouronic acid molecules, esterified by sulphuric acid (Plate XXX: Fig. 85). It is a white or lightly coloured, amorphous powder and highly soluble in water. The aqueous solution of the sodium salt is neutral. It is standardised to contain 130 units/mg. or 650 Howell units.

- Actions.** (a) Heparin with a confactor (alpha globulin) forms a complex which has a powerful antithrombic action. This chiefly accounts for its powerful anticoagulant activity, 10 mg. of sodium heparin preventing the clotting of 5 litres of plasma for 4 hours at 37°C.
- (b) With a cofactor, it is also believed to have an antiproteolytic action. It prevents formation of thromboplastin and agglutination of platelets.
- (c) It dilates coronary vessels. There are evidences of subjective improvement but objective evidences are disputed.
- (d) It is believed to clear alimentary lipaemia and redistribute plasma lipoprotein factors in the body.
- (e) The dosage of heparin depends on the need of the patient and his clotting time has to be checked 2-3 times a day.
- (f) Given orally, it is ineffective, given subcutaneously, it causes pain and irritation and given intramuscularly, haematoma is produced. So it is usually given I.V. by either slow continuous drip method or intermittently.
- (g) *Dose:* 10-15 mg/hr. for the first two days and then 5-10 mg/hr in subsequent days.

Because of its short duration of action, its frequent administration becomes a necessity and that may induce haemorrhagic tendency, purpura, echymosis, haematuria and bleeding from the sites of operations. *Protamine:* 5-10 ml. 1% sol., I.V., acts as a *specific antagonist*, counteracting heparin effects promptly and effectively.

- Uses.** (a) Prevention of clotting during transfusion.
- (b) Combating phlebitis, thrombophlebitis, pulmonary embolism and coronary thrombosis.
- (c) Prevention of postoperative thrombin formation in the surgery of blood vessels.
- (d) Prevention of clotting of blood in animal experimentation.

DICOUMAROL

Bis-hydroxy coumarin was isolated in 1941 from the spoiled sweet clover, which caused haemorrhagic diatesis in cattles. It was synthesised later. It is a colourless, crystalline solid and insoluble powder. Potassium hydroxide splits it into two molecules of salicylic acid. Its absorption is fair after oral administration.

Action. It depresses the coagulability of blood, which action develops slowly. This occurs only after an adequate concentration of the drug has been reached in the liver, where it acts as an *antagonist* of *vitamin K*, which plays its part in the synthesis of prothrombin. The antagonism is explained on the basis of similarity in chemical structure. Dicoumarol diminishes prothrombin and the stable factor at the level of the blood. Its chemical structure is shown in Plate XXX: Fig. 84).

Toxicity. (a) Haemorrhagic manifestations as in the case of other anticoagulants.
 (b) Hepatic damage observed in animals.
 (c) In high doses, myocardial depression.

	<i>Heparin</i>	<i>Dicoumarol</i>
Mode of action	Antithrombin and antiprothrombin activities.	Depression of prothrombin synthesis.
Control tests needed during therapy	Simple coagulogram at bedside.	Precise determination of prothrombin time in laboratory.
Response	Prompt, consistent, predictable and short actions.	Delayed but lasting response. onset after about 24 hrs.
Route	I.V.	Oral
Contraindication	Active bleeding.	Active bleeding, hepatic and renal diseases.
Antagonist	Protamine or whole blood transfusion.	Vitamin K or whole blood transfusion.

Uses. For prevention of thrombosis in post operative thrombophlebitis, pulmonary embolism and coronary occlusion. Use only if facilities for prothrombin time determination are available. It is given in a dose of 200-300 mg/orally, on the *first day*. On the *second day*, if

prothrombin time is more than 25%, 100-200 mg. dose is repeated. On *subsequent days*, 100-200 mg. only, if prothrombin time is above 25%.

Dicoumarol lessens the embolic phenomenon and mortality rate in coronary thrombosis. The use of anticoagulant therapy in coronary insufficiency with infarction, is advocated.

TROMEXAN

Ethylbis Coumacetate. It is a synthetic anticoagulant of the coumarin series and has replaced dicoumarol, which it closely resembles, in all respects and in clinical practice also. Colourless, crystalline powder and fairly soluble in water. It is rapidly and completely absorbed from the G.I. tract. Its maximum action is produced in 28-36 hours, which lasts for 60-72 hours. *Dose:* Initially 1.5 gm./os, followed by 0.6-0.9 gm./daily.

CUMOPYRAN

Chemically related to dicoumarol to which it resembles in pharmacological actions but its actions start earlier and persist longer. It is 3 times more potent than dicoumarol but is much less toxic. *Dose:* Initially, 100-200 mg. orally and 12.5-50 mg. next day, if prothrombin time is more than 25% of the normal.

WARFARIN SODIUM

Chemically it is coumadin and is a coumarine derivative. It is a potent anticoagulant, 40 times more potent than dicoumarol, to which, it resembles, in all other respects. Its *advantages* are: (a) rapidity of action, (b) greater predictability of responses, (c) shorter latent period of action, due to the I.V. route, (d) longer duration of action, (e) fewer resistant cases. *Dose:* Orally, 25-50 mg/per day upto the 3rd day; 75 mg. I.V. It prolongs prothrombin time to 25-45 sec. in 12-18 hours and the action persists for 6 days.

MARCUMAR

A new potent anticoagulant of the series of 4-hydroxy coumarin derivative. White, crystalline powder and sparingly soluble in water. After a single oral dose, hypo-prothrombinaemia persists for 5 days. It is cumulative like other coumarin derivatives. *Dose:* 21 mg./1st day; 9 mg./2nd day and 3 mg./daily, subsequently. It resembles dicoumarol and tromexan, in all respects.

PHENANDIONE OR HEDULIN

It is an oral anticoagulant which has a rapid and short action and consequently, no cumulation. Vitamin K effectively counteracts its effects, the maximum action occurring after 28 hours. *Dose:* Initially, 200-300 mg., followed by 50-100 mg./day. It causes minimum haemorrhagic tendencies but agranulocytosis and sensitivity reactions have sometimes been seen.

DEPAXIN

It is an inandione derivative, with a rapid onset of hypothermbinaemia and in doses of 50 mg. lowers prothrombin time effectively, in 48 hours. It is a relatively nontoxic drug and its action is predictable. *Dose:* 1st day: 30 mg; 2nd day: 15 mg. followed by 2.5-5 mg./day.

DOSE AND TIME RELATIONS OF ANTICOAGULANTS

<i>Drug</i>	<i>Average dose in mg.</i>		<i>Time involved and duration of effect in hours after administration.</i>	
	<i>Initial</i>	<i>Maintenance</i>	<i>Time involved</i>	<i>Duration</i>
Heparin	10-15	5-10	1/12-1/6	3
Dicoumarol	200-300	25-100	48-72	48-120
Tromexan	1200-1500	150-900	18-28	24-72
Marcoumar	18-21	3-12	48	168
Cumopyran	150	50-75	—	—
Phenandione	150-300	25-100	18-48	24-72
Dipaxin	20-30	2-5	24-72	144

ANTI-COAGULANT THERAPY

This is an important adjunct to the therapy of a number of medical and surgical conditions. The *major* medical conditions are (a) myocardial infarction, (b) thrombosis and embolism, as well as (c) operative procedures involving arterial repair, grafting, thrombo-emblectomy, thromboendarterectomy.

The principal aim and object of use of established anticoagulants are mostly the prevention and arrest of thrombus formation in the coronary vessels, as well as, intra-cardiac mural thrombosis, phlebotrombosis in leg veins and pulmonary embolism.

Drug therapy comprises controlled uses of short and long acting anticoagulants of heparin and dicoumarol series, for a specified period.

Heparin: is given in doses of 10,000 units (100 mg) I.V. every 6-8 hours, for the first two days, with *Dindevan*, a phenendion derivative: 150-200 mg. on the *first day*, 100 mg. on the *2nd day* and a *maintenance dose* of 50 to 100 mg./day/orally, or *Warfarin Na*: 25 to 40 mg. orally *initially*, followed by a *maintenance dose* of 5 to 15 mg. daily.

During the therapy, a close watch has to be kept on the prothrombin time which should be kept at 25 to 30% of the normal. Signs of haemorrhage in skin, urine, stool and sputum, should be looked for and timely *antidoted* by *Protamine sulphate* I.V. for Heparin, and *Vitamin K*: I.V. or K_1 orally, for the coumarine derivatives.

The *contraindications* of anticoagulant therapy are many: peptic ulcer, liver and kidney diseases, retinopathy, malignant hypertension, pregnancy, previous cerebro-vascular accidents and any haematological disorder.

SCLEROSING AGENTS

These drugs, in suitable solutions, on local injection, irritate the intima of the veins, from thrombii, produce sclerosis and improve varicose veins. They are good adjuncts to operational therapy and many cases improve by this treatment only.

Sodium Salicylate: 20, 30, & 40%—10 ml. 5 ml. & 3 ml. respectively, in successive injections, in the above order.

Injectio Quinine et Urethane: (quinine—12.5%, urethane—6.5% and chlorocresol—0.1%). *Dose*: gradually increasing from 0.5—5.0 ml. May give allergic reactions and is *contraindicated* in acute phlebitis, deep thrombosis, C.V. disease and pregnancy.

Injectio Sodium Morrhuetis: 5% Sol. *Dose*: 0.5—5.0 ml.

Mono-Ethanol Amine Oleate: 5% Sol. *Dose*: 1—3 ml. A very satisfactory preparation for varicosity. It is non-irritating and has no contraindication.

Sodium Tetradecyl Sulphate (Sodium Sortadecol): A white, waxy, odourless solid, soluble in water and 1, 3 and 5% sols. are employed, depending on the size of the vein. Not more than 1 ml. should be injected at one site, the *total dose* never exceeding 6 ml. of a 5% solution. It is a surface active wetting agent, having sclerosing properties. It has been used in varicose veins and haemorrhoids. Paravenous injection is painful and causes tissue sloughing.

Sodium Psyllate or Slynasol: The solution of the fatty acids of the seeds of *Plantago ovata*: 5% solution, containing 2% of benzyl alcohol, is used as a sclerosing agent. For testing the sensitivity, an *initial dose* of 0.5 ml. is injected. The *total single dose* is 6 ml. of a 5% solution.

FIBRINOLYTIC ENZYMES

There are a few newer types of therapeutic agents which have been discovered in recent years, with the specific purpose of exploring the possibility of their dissociating the fibrinous tissues and thus acting as a type of *physiological cure* for the healing of ulcers and wounds. In the present stage of our knowledge, three such agents: *streptokinase*, *streptodarnase* and their combination *varidase*, are available for use. Though their roles have not yet been achieved, this being a novel approach of study, it is likely that better drugs from similar sources, will be available in future to meet the needs of the patients.

Streptokinase: It is derived from nonpathogenic bacteria which activate plasminogen in the human serum, lyse fibrin and dissolve blood clots.

Streptodarnase: It is also an enzyme, which liquifies protein complex, deoxyribose-nucleotide, imparting stringy, slimy, viscous characteristic to the pus and purulent exudates.

Varidase: It is a preparation which contains both these enzymes. It is derived from the Group C haemolytic streptococci.

- (a) Varidase has no action on living cells and can be introduced into body cavities or applied locally.
- (b) It is used in surgery and in skin grafting, to remove dead tissues and hasten repairs. Its combination with antibiotics is desirable.
- (c) It has been used in haemothorax, empyema, osteomyelitis, severe burns, tubercular sinuses and abscesses.

- (d) Commercial preparation contains 100,000 units of streptokinase and 25,000 units of streptodarnase. It is dissolved in 20 ml. of fluid, just before use. The dose depends upon the amount of coagulum or pus. It is also available in the form of a jelly, for local application.
- (e) Recently its use has been suggested in the treatment of oedema, associated with infection and trauma, when the oedema fluid contains a high concentration of fibrin.
- (f) Varidase is an effective 'physiological curetta' and along with antibiotics, controls superficial and deep tissue infections. It is contraindicated in gangrene. Untoward effects are febrile and allergic reactions in certain cases.

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SECTION

VII

BODY FLUIDS, IONS, METALS, METAL ANTAGONISTS AND RADIO ISOTOPES

CHAPTER

32

BODY FLUIDS, IONS AND BLOOD SUBSTITUTES

BODY FLUIDS, THEIR COMPOSITION AND DISTRIBUTION. BUFFERING SYSTEM, ACIDOSIS AND ALKALOSIS. WATER METABOLISM, DEHYDRATION AND WATER INTOXICATION. PARENTERAL FLUID THERAPY

[Water represents two-thirds of the body weight and is a very important constituent of the human body. Its high solvent power and dielectric constant promote many physiological functions and reactions, ideally. It is distributed as *intracellular*, *extracellular* and *transcellular* fluids and maintains water-ionic balance. The *acid-base equilibrium* is regulated by a series of *buffering systems* viz. bicarbonate—carbonic acid, protein, haemoglobin and phosphate buffers. The functions of the lungs and the kidneys are of paramount importance. Any disturbances in the acid-base equilibrium, is reflected by the causation of different types of *acidosis* and *alkalosis*, which may be of respiratory or metabolic nature, affecting sodium and potassium balances. These conditions are to be set right etiologically .

Water metabolism is disturbed in a number of conditions, producing either intoxication or dehydration, for which latter, blood and blood substitutes are used. These may be whole blood, saline, plasma—in liquid or dry form, high molecular plasma expanders, dextran, PVP and oxypolygelatine, which are used both as substitutes, as well as, therapeutic agents, in haemorrhages, dehydration states, peripheral vascular failure, shock like conditions, anaemia, cerebral oedema or in comatose conditions.]

Body Fluids: Water is an important constituent of the animal body and represents nearly two-thirds of the total body weight. It furnishes the aqueous milieu, within which, the life processes occur. It seems that life started from the aqueous environment and during its evolution, the fluid medium was enclosed by a protective water-proof layer of keratin in skin. Water, in a sense, is more essential than even food,

inasmuch as, an individual cannot survive even for a short period without it. Death usually results when about 20% of the body fluid is lost.

Water possesses a number of physical and chemical properties which promote its physiological activities — high solvent power permitting the formation of solutions, high dielectric constant, facilitating the occurrence of reactions, velocity, heat insulation etc. These are some of the important properties of water, utilised for maintaining the efficient regulation of *homoeostasis*. It is related to the intake and metabolism of foods and minerals and is controlled by C.N.S., heart, lungs, G.I. tract, kidney and also to a remarkable extent the cell membrane. Derangement in any one of the above systems, imposes extra load on others, which requires immediate rectification. For all these, exact knowledge about water balance, its composition and distribution in body fluids, is essential.

Distribution: Water constituting about 67% of body weight, is distributed as below:

Extracellular water — This represents 25% of bodyweight and comprises:

- (i) Circulatory fluid of plasma — 5%
- (ii) Interstitial fluid — 20%

Intracellular water — It represents 50% of bodyweight and is about 35 litres.

Transcellular water — This is only 2.5% of the total body weight and comprises G.I. and respiratory tracts, glandular, C.S.F. and aqueous humor fluids.

Intracellular and extracellular fluids have similar osmotic pressures, because of the need for free diffusion of water across the cell membrane. But they differ in pH and composition.

Composition: There is a vast difference in the electrolytic composition of the two main compartments. The extracellular fluid is rich in sodium chloride and bicarbonate and has also a small amount of protein. In contrast to this, potassium, magnesium, phosphate and proteins are the major constituents of the cellular fluid. The chief distinction between interstitial fluid and plasma, is in higher concentrations of proteins in the latter.

Total body volume of water	—	47–61%
Extracellular fluid.	—	16–18%
Plasma volume.	—	4–5%

Extracellular Na ⁺	—	145 mEq/lit.
Extracellular Cl ⁻	—	100 mEq/lit.
Extracellular K ⁺	—	5 mEq/lit.
Intracellular Na ⁺	—	26 mEq/lit.
Intracellular K ⁺	—	150 mEq/lit.

Water and Ionic Balance: The balance between the two compartments is maintained by the active transport, osmotic pressure and cell permeability of ions.

- (a) Active transport of ions requires high energy bonds of ATP, which is converted to work by ATPase.
- (b) The osmotic pressure in both the compartments of body fluids is the same, in spite of varying compositions and there is free permeability of water. Any change in osmality in one compartment results in net movement of water, until the fluids in the two compartments, are in iso-osmality.
- (c) Selective ion permeability of the cellular membrane hinders the diffusion of plasma proteins through capillary wall and holds water in body by osmotic pressure.
- (d) Water excretion is controlled by the posterior pituitary body through the elaboration of A.D.H.
- (e) The major responsibility for the maintenance of volume and electrolyte composition of body fluids rests with the kidneys. The renal tubules return to the circulation, the requisite amount of water and electrolyte, necessary to maintain the composition of extracellular fluid. By adjusting the concentration of extracellular sodium and potassium within narrow limits, the kidneys also indirectly control the volume and composition of the intracellular fluid and help in the maintenance of pH of body fluids. Any disturbance in volume and composition of water, such as loss of blood or plasma or effects of certain drugs, diseases and inadequate or excessive intake, may result in—(i) dehydration or even (ii) overhydration.

Acid-Base Disturbances: The pH of arterial blood is maintained within narrow limits in healthy subjects at values between 7.35—7.45. The pH of the intracellular fluid is about 7.00 and that of extracellular fluid—7.4. Accumulation of hydrogen ions lowers the pH and causes *acidosis*. On the other hand, loss of hydrogen ions, raises the pH and produces *alkalosis*. Both these conditions are ultimately corrected by the lungs, kidneys and various buffer systems.

Buffer Systems: They control the variations in pH by adjusting the gain or loss of hydrogen ions. The buffer system comprises a weak acid or a base and its salt. The addition of a strong acid to buffered solution leads to the replacement of the weak acid by the strong one, which reduces the number of free hydrogen ions and in this way, a variation in the pH is limited. The pH of the body fluids is controlled by the following buffer systems:

- (a) Sodium bicarbonate—carbonic acid system, (b) Proteins, (c) Haemoglobin and (d) Phosphate.

Bicarbonate—carbonic acid buffers: The main buffer system of the plasma is carbonic acid—bicarbonate, pH being dependent on the relative proportion of each, as per Henderson-Hasselbach equation:

$$\text{pH} = 6.1 + \log \frac{\text{B.HCO}_3}{\text{H.HCO}_3}$$

It is easily and efficiently regulated by the renal function and pulmonary ventilation, by altering the bicarbonate concentration in extracellular fluid and converting the CO_2 into carbonic acid. The hydration of carbon dioxide ($\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3$) depends on its tension i.e. (PCO_2) in the blood, which is determined by CO_2 production at the tissue level and its elimination through the lungs.

Protein buffers: These are polybasic polyacids of very great complexities. Like aminoacids, polypeptides and phospholipids, they are amphoteric electrolytes which can act both as hydrogen donors and acceptors, depending upon the hydrogen ion concentration of the solution. The isoelectric point of most of the proteins is below the pH of 7.0 and they therefore act as hydrogen ion donors within the physiological range. As weak acids, they function as buffers in the presence of their salts. Further, proteins participate in the acid-base balance by forming carbamino compounds, directly, with carbonic acid— $\text{R-NH}_2 + \text{CO}_2 \rightleftharpoons \text{R-NHCOO}^- + \text{H}^+$

Haemoglobin buffers: They control hydrogen ion concentration in three ways—(a) as a protein, (b) as a weak acid, forming buffer in the presence of its salt and (c) by changing its character as an acid, as it loses or gains oxygen. Reduced haemoglobin, compared to oxyhaemoglobin, is a weaker acid. The change from oxyhaemoglobin to reduced haemoglobin reduces H^+ ions from the solution. Haemoglobin thus plays a unique role in the acid-base balance, by increasing its affinity for both CO_2 and hydrogen ions, as it loses oxygen. It

permits the transport of CO_2 and H^+ , generated at the tissue level, from the periphery, to the areas of elimination.

Phosphate buffers: disodium and monosodium phosphates ($\text{Na}_2\text{-HPO}_4\text{NaH}_2\text{PO}_4$) are effective buffer systems within the physiological pH range, but its low concentration in ECF, limits the value. Depending on its concentration, it however determines the buffering capacity of urine and thus excretion of H^+ ions.

Phosphate esters : organic anions, contained within the cells are weak acids and also act as buffers. Because potassium is predominant an intracellular cation, its deficiency leads to the accumulation of sodium and H^+ ions, which results in changes in the intracellular pH.

Role of Lungs and Kidneys: Both of them are grossly involved in the regulation of 'acid-base balance', in the body.

Respiratory regulation: Lungs minimise the acid-base disturbances by eliminating more acid as CO_2 , by adjusting pulmonary ventilatory exchanges.

Renal regulation: Acid-base equilibrium is maintained by the renal mechanism by varying the rate of excretion of hydrogen and selectively reabsorbing the cations and anions. Hydrogen is obtained from carbonic acid, formed from CO_2 and H_2O by carbonic anhydrase in the tubular cells and is exchanged for Na^+ . Bicarbonate, combined with sodium, is returned to the extracellular fluid.

Types of Acidosis and Alkalosis: There are four types of acid-base disturbances of clinical importance — Respiratory acidosis and alkalosis; Metabolic acidosis and alkalosis.

(a) **Respiratory acidosis:** Retention of CO_2 due to improper ventilation is the primary cause. There is a fall in pH, rise in CO_2 content of the plasma and an increase in PCO_2 .

The hypoventilation should be checked by giving oxygen and by mechanical respiratory devices. Diamox, salicylates and ethamivan are also useful.

Diamox: induces a fall in pH due to the urinary excretion of NaHCO_3 , which serves to stimulate the respiration and improve the ventilation. Aspirin and sodium salicylate increase the sensitivity of the respiratory centres to CO_2 . **Ethamivan** (vanillic acid diethylamide) improves ventilatory exchanges by increasing the depth and rate of respiration.

(b) **Respiratory alkalosis:** In this case, there is an increased excretion of CO_2 via the lungs, due to hyperventilation. It is usually the outcome of an emotional disorder or effect of a drug like salicylate. There is rise in plasma pH and decrease in PCO_2 . Therapeutic measures

include the use of sedatives along with the breathing of a gas mixture, with 5% CO₂.

(c) *Metabolic acidosis*: This results either from the loss of bicarbonate or from a metabolic disorder such as diabetic ketosis and renal insufficiency. Acidifying agents like ammonium chloride, can also produce this disturbance. There is a fall in plasma pH and in total CO₂ content and PCO₂. Alkalinising agents, along with specific therapy for different types of acidosis, are used. Solutions of sodium bicarbonate or lactate or citrate are indicated in this condition.

(d) *Metabolic alkalosis*: This is characterised by an increase in the plasma bicarbonate and pH and can be induced by a loss of hydrogen ions by administration of sodium bicarbonate or citrate or by potassium loss with use of diuretics. The treatment of metabolic alkalosis requires the causative factor to be corrected and modified. Administration of potassium and ammonium chloride serves, useful purposes in certain cases.

SODIUM BALANCE

The principal ion of the extracellular fluid (ECF) is sodium and because of its easy diffusibility, it governs the tonicity of all fluid compartments. Due to a very effective control on the part of the kidneys, variations in the intake of sodium are effectively compensated and normal tonicity of body fluids is maintained either by an excessive water retention or loss, as the case may be. Changes in sodium concentration is mostly an index of altered body fluid content than an actual change in the electrolyte.

Sodium deficit in the body can occur in adrenal insufficiency, in which, mineralo-corticoids, responsible for reabsorbing sodium, are secreted poorly. Salt wasting forms of nephritis, recovery after acute renal failure and diuretics can also cause excessive sodium loss. This is accompanied by a proportionate loss of water and results in reduced body fluid (ECF) dehydration, fall of blood pressure, reduced glomerular filtration with a consequent rise of blood urea. Unlike dehydration caused by poor water intake, here there is no change in sodium concentration but only an elevated serum protein and hematocrit.

Hyponatraemia: differs from the above as there is reduction of sodium in the blood. It is sometimes seen in acute infections and lung cancer and the cause is not known. It cannot occur from an excessive water intake or adrenal insufficiency. Perhaps there is increased secre-

tion of ADH due to tumour, leading to an excessive water retention. The osmotic pressure of blood is low in this state.

Sodium excess occurs from abnormal retention, as in congestive cardiac failure and cirrhosis of liver. Simultaneous fluid retention helps to swell up ECF and the blood may even show low sodium concentration, as the ion may accumulate in other tissues like bone.

Hypernatraemia, with increased osmotic pressure of the blood, is not due to water deficit but due to disturbed osmo-regulation, as in some intracranial tumours.

Water and sodium balances are not separate entities as shown by the fact that excessive water intake during antidiuresis by pitressin and surgical trauma, leads to an increased sodium excretion, even though the sodium concentration in the ECF is low because of dilution. This hyponatraemia therefore, differs from that in CCF by the fact that the urinary sodium is high and from adrenal insufficiency, in which the serum potassium is unaltered and the non-protein nitrogen in plasma is low. The condition is treated best by water restriction.

POTASSIUM BALANCE

Derangement of potassium metabolism may lead to the alteration in water and acid-base balance. Potassium is an intracellular cation and its blood level does not always give a correct idea about an existing excess or deficiency. Serum potassium levels may increase in dehydration and acidosis and lowered in alkalosis, without any alteration in the body level.

Potassium deficit occurs due to deficient intake, prolonged intravenous fluid therapy, prolonged diarrhoea, diuretics, recovery stage of acute renal failure and diabetic coma.

The symptoms and signs are—motor weakness, ECG changes, alkalosis and reversible defect in water reabsorption, leading to polyurea, thirst and dehydration. The alkalosis is due to the preferential absorption of bicarbonates in the kidney.

These conditions are amenable to medication with oral or parenteral potassium. The latter is to be done carefully because of the possibility of causing cardiac standstill if the dose is high.

Potassium excess can occur in chronic renal diseases and acute renal failure, where the ability of the kidneys to clear out potassium, is reduced. Transfusion of stored blood in patients with poor kidney function can also cause this, because in stored blood, potassium leaks out of the red blood corpuscles, into the plasma.

Typical ECG changes help in diagnosing potassium excess and this

should be corrected urgently to prevent cardiac arrest, by the use of cation exchange resin, artificial dialysis (kidney) and administration of I.V. glucose and insulin. The last method helps by promoting the entry of glycogen into cells and along with 1 gm. of glycogen, 0.4 mm. of potassium also enters into it.

MANAGEMENT OF ACIDOSIS, ALKALOSIS AND COMAS

Acidosis: It is of several types and may result from (a) diabetes mellitus, (b) starvation (c) diarrhoea (d) cyclic vomiting (e) nephritis (f) nephrosis (g) infectious diseases (h) toxic effects of morphia, barbiturates, hydrochloric acid, sulphonamides and salicylates and (i) pregnancy and toxæmias of pregnancy.

Its management comprises (a) general as well as (b) special measures:

General: (i) gastric lavage, (ii) use of analeptics, if needed (iii) parenteral administration of 5% glucose-saline (iv) use of alkalies — sodabcarb or sodium lactate along with glucose and saline.

Special: Treatment of underlying conditions:

- (a) In diabetic coma, — insulin, glucose, saline, potassium chloride and sodium phosphate.
- (b) In diarrhoea and vomiting, — parenteral fluid along with sodium bicarbonate and lactate.
- (c) In nephritis and nephrosis, — same as above.
- (d) In poisoning cases, — stomach wash: parenteral fluid therapy as above and specific antidotes.

Alkalosis: It is frequently seen in (a) high fever (b) anoxemia (c) encephalitis (d) hyperemesis (e) peptic ulcer (f) sulphonamide therapy and (g) radiation therapy.

Management comprises: (a) gastric lavage (b) replacement of chlorides (c) stopping alkalies and giving magnesium trisilicate, aluminium hydroxide gel, large amounts of fluids — orally, parenterally and rectally and also administration of blood plasma and whole blood, as and when necessary.

Coma: A state of unnatural deep and prolonged unconsciousness, accompanied by slow breathing and often ending in death. The underlying causes are:

- (a) Infective conditions — typhoid, malaria, influenza, diphtheria dysentery and cholera.
- (b) Metabolic disorders — diabetes, uremia, Addison's and Raynaud's diseases.
- (c) Inflammatory disorders — meningitis, encephalitis.
- (d) Drug poisoning — barbiturates, morphine, insulin, alcohol, carbon monoxide and carbolic acid.
- (e) Vascular lesions — haemorrhage and thrombosis.

Their management comprises (a) general and (b) specific therapies, on etiological basis.

Use of O_2 and CO_2 under pressure, respiratory stimulants — coramine and metrazol, parenteral fluids—5% glucose and 0.9% saline, cardiac stimulants, diuretics and also treatment of causes, depending on the etiology of the disease.

METABOLISM OF WATER

(a) After ingestion of water, the ionic equilibrium in the intestine is changed and the fluid enters the circulation and goes to the extracellular space. Expansion of volume with subsequent lowering of sodium concentration creates a decrease in effective osmality and posterior pituitary hormone. This is accompanied by a movement of water from the extracellular to the intracellular space, till the two fluids, once again, become iso-osmotic.

(b) Administration of sodium salt increases its concentration in the extracellular fluid. This promotes redistribution of water from the cells to the extracellular fluid, till isotonicity is established.

The above is also applicable to the steady state of distribution of the volume between interstitial and plasma fluid compartments.

(c) The capillary membrane is relatively impermeable to plasma proteins but not to water, electrolytes and small molecules. The proteins in solution within the capillary lumen, exert an osmotic force (oncotic pressure), which results in the passage of fluids from the interstitial space into the circulation. This is opposed by the hydrostatic pressure of the circulating fluid within the capillaries. Thus the fluid continues to leave the capillary as long as the hydrostatic pressure within the vessels is greater than the osmotic pressure, exerted by the plasma proteins. Fluid enters the circulation in the opposite conditions.

(d) At the arterial end of the capillary, the hydrostatic pressure is more and therefore the fluid leaves the vessels and enters into the

interstitial fluid. At the venous end, the osmotic pressure is greater and hence the same amount of fluid is absorbed back, inside the capillaries.

Therapeutic implications of this internal exchanges of water is that for increasing the plasma volume, administration of a preparations containing colloidal agents is necessary. The administration of saline to a person, who has lost blood, expands the extracellular fluid, which is then confined to the interstitial compartment.

Water Intoxication: This occurs when the absorption of water exceeds its excretion from the body, resulting in haemolysis and cellular oedema. There is a decrease in the concentration of all the constituents of the body fluids. Overhydration occurs in patients receiving (a) intravenous injections in whom the water intake is in excess of the excretory capacity, (b) from vasopressin treatment and (c) in congestive heart failure.

Administration of water by injection will cause haemolysis at the site of administration and for that, isotonic solution of glucose or saline is used.

Dehydration: It is more frequent and is a very serious condition. It is the reverse process of water intoxication. There is a varying degree of water and sodium loss in different conditions of dehydration. Invisible perspiration, sweat, G.I. tract, urine, intake of sodium, potassium and magnesium all control the loss of or accumulation of water in the body. This may be due to the lack or insensitivity to the anti-diuretic hormone as in diabetes insipidus. Potassium deficiency, hypercalcaemia and sickle cell anaemia also produce dehydration states. Whole blood, blood substitutes and plasma expanders are used for combating these conditions, as detailed below.

BLOOD SUBSTITUTES

These substances, given intravenously, in cases of loss of blood, shock, peripheral vascular failure, and dehydration, restore the volume and osmotic pressure of blood and supply essential constituents to the body. They elevate blood pressure, effectively combat the impending circulatory failure and promptly improve the condition of the patient, at least, as a temporary measure, allowing the system to mobilise its own resources for a more sustained recovery.

The substances in use, are many — salines, whole or cadaver blood, plasma in dry and liquid forms, recently introduced large molecular substances like dextran and polyvinyl-pyrrolidone (PVP) and gelatin

preparations. The ideas underlying the use of this latter group of agents are that as they do not easily pass out of the circulation as a result of glomerular filtration, they are capable of producing prolonged action without kidney or any other organ toxicity.

Salines: Sodium, though present in the body in ionic form, is less active than the salts, which latter, by virtue of their osmotic pressure, play an important physical role as blood substitute in haemorrhages, dehydration due to vomiting and diarrhoea, postoperative shock and also for lowering intracranial tension.

Hypertonic: It is largely used in toxaemias and cholera. In this form, the fluid is drawn from tissues and the blood volume consequently is maintained for a longer period. In its composition, besides sodium chloride, potassium and calcium chlorides and sodium bicarbonate, are also added, with a view to correct the electrolyte imbalance and maintain the B.P. and the pH of blood at their proper levels and also to combat the acidosis.

Gum saline: This is another form of saline, in which, 6% of gum acacia, in purified form, is added, with a view to induce viscosity to the fluid, so that it could restore B.P. for a longer period and be slowly eliminated. However, in this colloidal state, acacia is sometimes deposited in liver and kidney glomeruli, producing toxic effects

Blood Transfusion: (a) It has been extensively used during the last 25 years, in shock conditions, surgical operations, burns, anaemias and severe sepsis.

(b) Whole blood, citrated blood, stored blood, cadaveric and placental blood, have all been used, the first two being the best.

(c) Blood transfusion makes up the volume loss and haemoglobin deficiencies and the oxygen carrying power also increases.

(d) Grouping, as well as, determining of Rh factor, are necessary. Malaria, syphilis and filaria may be transmitted through the infected blood of the donor and consequently, the donors should be thoroughly investigated from all these points of view.

The transfusion of whole blood often presents the difficulty of scarcity of adequate number of donors in an emergency period. Therefore, organisation of *Blood Banks* for storing blood in adequate quantities and under ideal conditions, is essential. Nevertheless, long storage and transport from one place to another, spoil some of its properties.

Plasma and Serum Transfusion: This is less dangerous and equally

effective in — (a) shock (b) severe infections, supplying non-specific antibodies also, (c) hypoproteinaemias, as in nephrosis, liver diseases and fibrinogen deficiencies, (d) emergency treatment of acute haemorrhage. Its *advantages* are: (a) No cross-matching or typing is necessary and (b) ready stock is more easily available, as these can be stored for longer periods.

The *disadvantages* are: (a) Storage and transport, as in the case of the whole blood, are essential and (b) prothrombin, complement and antibodies are unstable in long cold storage.

Dry Plasma: This is prepared by the processing of fresh plasma in a *lyovac* or *desivac*, converting the liquid plasma to the dry forms, without denaturing its proteins and increasing its toxicity. It is thus an improvement and a solution to many of the above shortcomings of liquid plasma and serum.

- (a) The process involves desiccation of frozen serum or plasma in high vacuum and is used for the preparation of other thermolabile biological products also.
- (b) The dry plasma or serum retains properties for 3-5 years. They contain specific and non-specific antibodies, complements, coagulating elements, $\frac{3}{5}$ of the platelets, which are essentially the same as in normal blood or fresh plasma.

It is available in powder form, in ampoules, yielding 250 cc. of fluid plasma in pyrogen free water. Its dose depends on the condition of patients — a few hundreds of millilitres each time. Records of 7 litres/11 days.

Dextran: also known as *epandex*, 'gentran' or 'plavolex', is a polysaccharide of high molecular weight, formed by the bacterial action of *leuonostoc mesenteroides* on the sucrose. Depending on the source and the method of preparation, the physical and chemical properties differ, but as a blood substitute, dextran having 75,000 molecular weight, is used. In 6% concentration, it is a pale, yellow straw coloured solution with a viscosity of 3.16 — 3.66 and osmotic pressure of 65-70 cms. of water. After slow I.V. infusion, 25-40% appears in the urine in the first 24 hours and 90% excreted in 10 days. A part of it is converted to glucose. It is a good blood substitute with prolonged action, due to its slow excretion. It retards tissue catabolism and thus nitrogen and phosphorus are spared in the body.

It is used in (a) peripheral vascular failure and (b) nephrosis, in

doses of 6% solution; 1% by volume of the body-weight and $\frac{1}{2}$ % thereafter, daily. Its *side-effects* are allergic manifestations, haemorrhagic tendencies and occasional liver and kidney damage. Elimination of impurities and preparation of uniform products with narrow spectrum of molecular weight, overcome these drawbacks. It should be used with caution in patients with pulmonary oedema and heart failure.

Polyvinylpyrrolidone (PVP, Periston): It is a synthetic, high molecular-weight polymer, formed by the combination of acetylene, ammonia and formaldehyde. Its average molecular weight is 40,000, viscosity 2.14—2.20 and osmotic pressure of injected material, 33-35 cm. of water. The solution is stable, non-toxic, nonpyrogenic and nonantigenic. A 3.5% solution in saline is used as blood substitute. Much of the material is retained by the kidney glomeruli and stored in the body for long periods, in skin, skeletal muscles and reticulo-endothelial system. It has been successfully used in various types of shock, as PVT alone or with blood and plasma, but further clinical assessment is necessary.

Gelatin: Recent investigations have indicated its disadvantages as blood substitute, due to the unknown fate of the unexcreted portion, interference with blood groupings and also solidification at room temperature. *Oxypolygelatin*, which has a high molecular weight and viscosity, does not have these drawbacks and has given better results than gelatin. A modified fluid gelatin, made of a special-type of gelatin for I.V. transfusion, is under trial.

PREPARATIONS AT A GLANCE

Normal saline	0.9% I.V.	Sodium bicarbonate solution	1.3% I.V.
Hypertonic saline	2.5-5% I.V.	Sodium lactate injection	1.9% I.V.
Glucose injection		Potassium chloride	3gm/125 ml.
(a) Isotonic	5% I.V.	Ammonium chloride sol	5.35gm/20 ml. IV.
(b) hypertonic	10-15% I.V.		
Glucose saline		Mannitol solution	25% I.V.
glucose	4.3%		
Na Cl	0.18% I.V.	Protein hydrolysate	5-10% I.V.
Dextran solution	6% in normal saline I.V.		

CHAPTER

33

PHARMACOLOGY OF CATIONS AND ANIONS

IONS OF ALKALI METALS. SODIUM, POTASSIUM, AMMONIUM, MAGNESIUM
AND CALCIUM. ACIDS AND SALTS. THEIR ACTIONS AND USES

[A large number of positively charged cations and negatively charged anions, not only play important physiological roles in the body but are also used as drugs, because of their important pharmacological actions. The role of sodium salt as saline — osmotic, in the blood and extracellular fluid, that of potassium intracellularly, in the functioning of cardiac muscle, muscular contractions and in the release of acetylcholine, at the nerve endings, are established. Similarly, ammonia, magnesium and calcium play their distinctive roles in the physio-pharmacology of the body. Quite often, their actions are synergistically, but sometime also antagonistically designed, so as to produce a delicately adjusted, balanced action, in the body, as an end-result.

If this is so for the positive ions, the same is the case with negative ions and their salts — hydrochlorides, nitrates, sulphates, acetates, citrates, phosphates and lactates. Some of the inorganic acids are irritant and escarotic and in dilute form, astringent and haemostatic. Hydrochloric acid dil. is used in hypochlorhydria, phosphoric acid and phosphates as nerve tonic, citrates and acetates as alkaliniser and diaphoretics, while some also as mild antiseptics.]

Elements or groupings which show electrical charges in a solution, are known as ions. If the charges are positive, the ion is called a *cation* and if negative, *anion*. The nature of the electrical charges and physio-chemical interactions, may determine the physio-chemical and pharmacological actions of many of these substances, which besides their role in the normal functioning of the body, are used therapeutically, for their actions in different diseases.

In this group, both the groups of the substances will be studied:

Cations: Na + (sodium), K + (potassium), NH₄+ (ammonium), Mg + (magnesium), Ca + (calcium) Li + (lithium) and Ba + (barium).

Anions: Cl⁻(chloride), SO₄⁻(sulphate), NO₃⁻(nitrate), PO₄⁻ (phosphate), I⁻(iodide), CH₃COO⁻(acetate),

$\left. \begin{array}{l} \text{COOH}^- \\ \text{COOH}^- \\ \text{COOH}^- \end{array} \right\} \text{ Citrate}$
 $\left. \begin{array}{l} \text{COOH}^- \\ \text{COOH}^- \end{array} \right\} \text{ oxalate}$

and $\left. \begin{array}{l} \text{COOH}^- \\ \text{CH}_3\text{COOH}^- \end{array} \right\} \text{ Tartrates}$

SODIUM

Sodium is an important constituent of the body. Normally, the body contains 70 gm. of sodium chloride, most of which is present in the plasma. The water-salt balance of the body is regulated by the post-pituitary body, as well as, by the excretory functions of the kidneys.

Preparations: Metallic sodium offers a large number of salts of diverse uses. These are:

- (a) Chloride — blood substitute,
- (b) Hydroxide — caustic,
- (c) Carbonate, bicarbonate and citrate — antacid,
- (d) Tartrate, phosphate and SO_4 — purgative,
- (e) Acid sodium phosphate — acidifier of urine.

Actions: Metallic sodium is pharmacologically inactive and the salts produce most of the actions. The important actions are:

Sodium chloride — the saline-osmotic, acts mostly on the blood volume. It is absorbed from the duodenum and the daily turnover is about 5-10 gm. It also plays an important part in the formation of hydrochloric acid in the stomach.

Normal saline — is used in shock and dehydration. If acidosis is present, sodium bicarbonate may be added but on autoclaving, it is converted to toxic carbonate.

Hypertonic saline — is used for cerebral oedema, pyloric stenosis and intestinal obstruction and as Roger's *procholera saline*, comprising sodium chloride — 8.00 gm., calcium chloride — 250 mg., potassium chloride — 400 mg. and squa ad — 0.5 litre I.V.

The antacid and purgative groups (bicarbonates and sulphate) will be dealt with in their respective chapters.

Sodium citrate: is easily absorbed from the intestine and converted into carbonate in the tissues, raising the alkali reserve. It is eliminated as bicarbonate, rendering urine alkaline. It is also a remote antacid, prevents coagulation of blood and curd formation in the milks of babies. *Dose*: 1-2 gm.

Acid sodium phosphate: The normal acid salt in urine, may be used in cases of *B. coli* infections and phosphaturia. *Dose*: 1-2 gm.

POTASSIUM

It is an important constituent of cell and intracellular fluid, as sodium is of plasma. It is present in vegetable and animal cells which are the

sources for its normal intake in the body. Potassium is abundantly present in striated muscles. It is increased in brain, during sleep and anaesthesia and is decreased in (i) diabetes (ii) Parkinson's disease (iii) myopathies (iv) paralysis and (v) delirium tremens.

Potassium is readily absorbed from the G.I. tract. Being the chief intracellular cation, it is treated as a foreign low-threshold substance in the plasma and is excreted easily in glomerular filtrate and reabsorbed and secreted by tubules, after maintaining the required balance. It also improves the motor nerve transmission, as observed in the treatment of familial palsies.

In *hypokalaemia*, there is a dilution of the extracellular reserve by water and glucose and oedema ensues from the shifting of extracellular potassium into cells. Alteration of pH of the body fluids also produces a potassium shift. External loss may be produced by adrenocorticoids, carbonic anhydrase inhibitors, vomiting, diarrhoea and ion exchange resins. On the other hand, inadequate urinary excretion and suprarenal insufficiencies, cause positive potassium balance.

Action: Potassium chloride, which produces ionic action of potassium on injection, causes toxic actions on heart and C.N.S.

- (a) On the heart, potassium causes depressed contractility, antagonised by calcium and lowered potassium level precipitates digitalis intoxication.
- (b) Potassium stimulates muscle contraction and depolarisation on local application on cardiac muscle fibres (acetylcholine endplate only). This stimulant action is not abolished by curare.
- (c) Release of acetylcholine at the nerve ending is associated with potassium diffusion from the nerve cells. The ion is necessary for acetylcholine synthesis without entering into any chemical reaction.

Uses: (a) The citrates, acetates, tartrates, bicarbonates and nitrates are used as diuretic and alkaliniser of urine. They may be used in ordinary fever as diaphoretic and diuretic and also in uric acid diathesis e.g. gout, as alkaliniser of acid urine. *Dose:* 1-2 gm.

(b) Potassium acid tartrate is a saline purgative and mild diuretic. The 'imperial drink' is used as a lemonade.

(c) Potassium chlorate gargle — 2%, is an oral antiseptic and astringent and acts by liberation of O_2 . The same is the case with potassium permanganate.

(d) Potassium chloride is used in familial paralysis and myasthenia gravis. Dose: 1-2 gm.

AMMONIUM

The radical has dual character:

- (a) Strongly alkaline, forming salts, similar to the alkali metals.
- (b) By liberation of ammonia gas from its compounds and acting as a stimulant and irritant.

Preparations liberating *free* NH_3 are: Ammonium chloride — 1-4 gm. Liq. ammon. acetatis fortis (57%) — 1-4 ml; dilutus (7%) — $7\frac{1}{2}$ -30 ml.

Uses: The acetate is converted into urea which acts as a diuretic. The chloride is a diuretic and acidifier of urine. It produces acidosis, raises blood calcium level and potentiates actions of mercurial diuretics. It is converted to NH_4^+ and Cl^- in the liver, the former producing diuresis and the latter combining with bicarbonate, produces acidosis.

MAGNESIUM

Like calcium, magnesium is an ion of considerable physio-pharmacological importance and is indispensable for life. In small concentrations, magnesium is essential for the functional integrity of the neuromuscular system and in higher concentration, it acts as a C.N.S. and neuromuscular depressant.

There are strong evidences that magnesium ion affects the activity of numerous enzyme systems — adenosine triphosphate, cholinesterase and cholineacetylase, though in the present state of our knowledge, it is not possible to explain all the actions of magnesium through the enzyme system.

Magnesium deprivation in animals produces vasodilatation, hyperirritability, cardiac arrhythmia, spasticity and tonic-clonic convulsions, corrected by administration of magnesium salts, in human beings. Parathyroid tetany has also been found to be associated with low plasma magnesium.

Fate: Like calcium, magnesium has a very uncertain absorption. It is somewhat enhanced by acid reaction in the upper duodenum but then

retarded by its alkalinity. It is converted to chloride and rapidly excreted. This is accelerated by calcium.

In serum, magnesium is present in a concentration of about 3 mg.%, of which, 80% is diffusible and the remainder, protein bound. Its concentration in R.B.C. and muscle cells is fairly high, while following the pattern of sodium. Its excretion is so rapid that oral administration of magnesium hardly raises the blood level, unless there is some renal damage affecting the glomerular filtration.

Actions: These are both (a) Local and (b) Systemic and of considerable importance.

Locally, magnesium salts act as antacid, cathartic and also mild local anaesthetic. Applied on isolated intestinal strips, magnesium chloride acts as an antispasmodic. Hypertonic magnesium sulphate, introduced into the duodenum, temporarily increases the flow of bile by relaxing the sphincter of oddi and thus helping in the emptying of gall bladder. However, it does not possess any choleric action.

Systemically, its actions involve a number of systems in experimental studies.

C. N. S. and neuromuscular junction: There is depression and curare like action. Nerve impulses to skeletal muscles are impaired and there is flaccid paralysis of muscles. It also affects B.P., respiration and other medullary centres. Most of the effects of magnesium are antagonised by calcium, which can displace magnesium from cell surfaces, at a critical ratio of 1:20.

C. V. system: Unlike C.N.S., myocardium is much less sensitive and in usual dosage, it is not depressed. In animal experimentation, its high plasma level produces slight tachycardia and minor changes in the T-wave and QRS complex; the heart eventually stopping in diastole. *Clinically*, it may depress impulse production in the ectopic foci and may thus be useful in paroxysmal tachycardia. It can also abolish extrasystoles, caused by full digitalisation.

Smooth muscles: magnesium acts as a weak antispasmodic and can even relax these muscles. The spasmolytic action also extends to the uterus, in which, oxytocic action can be antagonised by $MgCl_2$.

Toxic Effects: These are quite infrequent, because of uncertain absorption of some of the salts and also their rapid excretion from the body. In cases of high I.V. doses, there may be C.N.S. depression, fall of B.P. and respiratory failure, which should be treated by artificial respiration and I.V. calcium therapy.

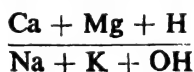
Preparations and uses: (a) *Magnesium oxide*, carbonate and trisilicate—0.6–4 gm. are used as antacids and adsorbent in gastric acidity.

(b) *Magnesium sulphate* — 4–6 gm. is used as purgative and cholagogue. 10 ml. of 25% sol. I.M. act as C.N.S. depressant in convulsive conditions, eclampsia, cardiac arrhythmia and ventricular fibrillation, in a concentration of 0.1 gm/litre.

(c) *Magnesium chloride* is used for experimental studies, occasionally in cardiac arrhythmia, in doses of 20 ml. 20% sol. I.V. and also in peritoneal and in haemodialyses in a solution of 0.1 gm/litre.

CALCIUM

General Considerations: (a) Calcium is an important constituent of the body, representing about 2% of total weight, of which, 99 % is present in bone, as phosphates and carbonates. It is also present in the extracellular fluid and is essential for the coagulation of blood. Unlike potassium, it decreases permeability of cell membranes and capillaries and in a balanced proportion with sodium, potassium and magnesium, it controls excitability and irritability of muscles and nerves—



(b) The minimum daily requirement of calcium in an adult is about 10 mg/kg, while children and lactating women require double this quantity. Because of its incomplete absorption, a daily intake of about 1.5 gm. is the optimum quantity. The main source of Ca is milk (human milk containing 0.035% and cow's milk 0.12%), in which, it is present as readily absorbable and active ionisable forms.

(c) The blood calcium level of 10 mg% is constant and is regulated by *parathormone* and *vitamin D*. In *rickets*, it is reduced, but not in *osteomalacia*. Body fluid contains 10–15 mg. % of Ca, part of which is *protein-bound* and non-dissociable and the rest in diffusible form as phosphate, carbonate and also in ionic forms, which is about 3–4 mg%. The blood and bone calciums are present in a state of equilibrium with a reciprocal relationship between the two, one making up the deficiency of the other, as and when, an occasion arises. The role of parathyroid hormone for this adjustment is of vital importance.

(d) Calcium deficiency in the body may be of — (i) *Acute type* as in tetany or (ii) *Chronic type*, as in rickets.

(i) *Tetany*: It is an acute syndrome in children, in which, there are characteristic carpo-pedal spasms, with convulsive seizures. The excitability of the neuromuscular system is grossly affected. In the

ratio, referred above, if any of the ions of Na, K or of OH of the denominator increase, tetany is produced and is relieved by an increase in any of the factors of the numerator. Relief is also obtainable by giving parathormone, Ca, Mg or acid producing ammonium chloride. In acidaemia, plasma calcium is in ionized state. Acidity favours the formation of soluble monocalcium phosphate and bicarbonate. The condition is also improved by the administration of any of the soluble salts like calcium gluconate I.V. The relief is immediate.

(ii) *Rickets*: In this condition, there is a gross deficiency of calcium metabolism, due to deficient functioning of Vitamin D. The blood is kept up at the expense of bones, resulting in softening and curvature of long bones, craneotabes, ricketty rasaries etc. The nutritional status of the child, as well as ossification of bones, is grossly affected. The management comprises adequate supply of vitamin D and calcium and also, correction of the faulty dietetic habit.

(e) In acute calcium deficiency, parathormone is too slow to act. In hypo-parathyroidism, there is increased retention of Ca and in hyper-parathyroidism, increased excretion. In the presence of Vitamin D, a positive calcium balance is restored and tricalcium phosphate is laid down, on the skeleton. Probably, local activity of phosphatase is important for the deposition of calcium in bones. This enzyme is present in high concentration in ossifying centres.

Metabolism: (a) Calcium salts are converted to chlorides in the stomach and to carbonates in the intestine, which latter, act as protactive, constipating and adsorbent.

(b) The absorption from intestine, which seldom exceeds 60% of the food content, is governed by several factors:

- (i) H-ion concentration in the gut: acidity favouring the absorption, while alkalinity changing it into insoluble salts and precipitating them in the intestine, hinder their absorption.
- (ii) Excess of phosphorus and phytic acid of cereals, disturb the absorption.
- (iii) Similarly, deficiency of vitamin D, by increasing the alkalinity of gut, also hinders its absorption.

(c) Calcium is best absorbed when given $\frac{1}{2}$ h. before or 4 h after the principal meals.

(d) Increase in serum calcium is dependent on its availability in soluble forms. In the blood, it is present as carbonate to the extent

Plate XXXI

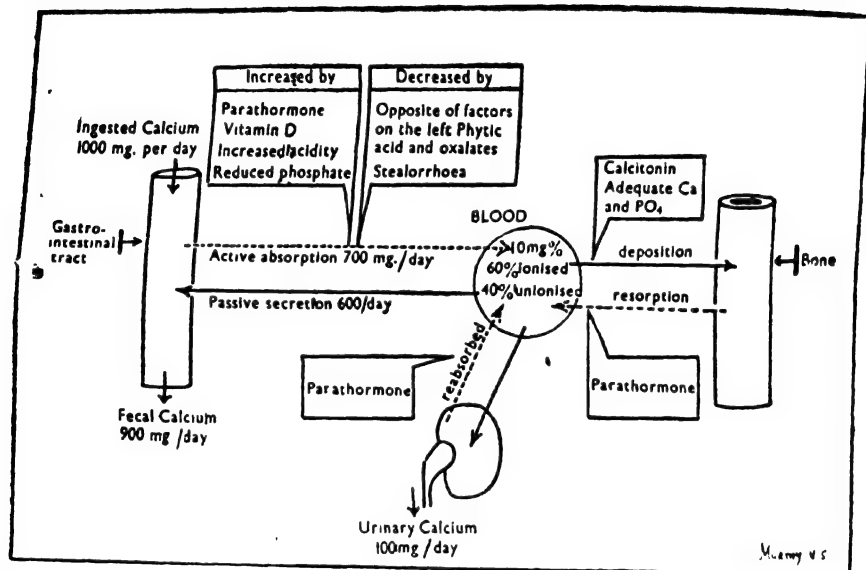


FIG. 86 Regulation of calcium metabolism

of 40% as chloride, 27% as gluconate — 9%, as lactate — 13% and 40% as tri-calcium phosphate.

(e) Calcium is excreted as phosphate in stool and as chloride in urine. The latter does not exceed 25-30%.

(f) The metabolism of calcium is diagrammatically shown in Plate XXXI, Fig. 86, from which, it is evident that Ca intake is favoured by the high Ca content in food, good Ca/P ratio and also by vitamin D. Its deposition in bones is influenced by high blood Ca and vitamin D levels. On the other hand, its removal from bones is favoured by low blood Ca, excess of parathormons and its excretion by high blood Ca levels.

Preparations:

Calcium chloride: — 0.6—2 gm. Calcium gluconate — 1—5 gm.
 Calcium phosphate — 0.8—2 gm. Calcium lactate — 0.3—2 gm.
 Calcium glycerophosphate. — 200—600 mg Calcium levulinate — 10% solution.

Calcium Gluconate is mostly used I.V. or I.M. — 10 ml. 10% solution. Calcium chloride and calcium lactate are used *orally*.

Actions: *Locally*, CaCO_3 is a protective, mild astringent and an anti-diarrhoeic, the dosage forms being — Calcium carbonate — 1-4 gm, Pulv. cret. aromatica: 1-4 gm., Liq. calcii. hydroxide — 30—120 gm.

Systemically: The important actions and uses of calcium are:

- (a) Control of nerve excitability through peripheral neuromuscular mechanism.
- (b) Maintenance of skeletal muscle integrity from increased ionised calcium, leading to increased contractility.
- (c) Antispasmodic action on smooth muscles and enhanced oxytocic effect from increased blood Ca level.
- (d) Maintenance of tone and contractibility and antagonism with the depressor effect of potassium.
- (e) On I.V. injection, temporary vagal stimulation and fibrillation, for which, slow I.V. injection, is advocated.
- (f) Ca acts synergistically to the toxic effect of digitalis.
- (g) Calcium is essential for the clotting of blood.
- (h) It decreases cellular permeability and may act as an anti-inflammatory and antiallergic agent. The antiallergic effect may be due to its sympathomimetic, as well as, its actions on the cellular permeability, being an important constituent of the intracellular cement substance.

(i) Calcium chloride produces diuresis.

Uses: These are numerous and have been detailed in their respective chapters. Some of them have scientific basis, while others are unconfirmed traditional uses. The prevalent uses of calcium salts are: (a) Tetany (b) Rickets (c) Anaphylactic condition, (d) Haemoptysis (e) Cardiac stimulant (f) Antacid (g) Diuretic (h) Liver protective (i) Lead poisoning and (j) Absorption of exudates.

BARIUM

It is a tricky metal, having salts widely varying in absorption and action. Any mistake in the selection of the exact salt, may sometimes produce disastrous toxic effects.

The *salts* of barium which find uses in therapeutics are:

- (i) Barium sulphate for X-ray diagnosis, in the form of barium meal. *Dose:* is variable and the drug is usually mixed in corn flour, in the proportion of 1 : 3. *Usual Dose* — 2-40 ozs.
- (ii) Barium chloride for systemic administration. *Dose:* 30-50 mg/OS.
- (iii) Barium sulphide as depilator — 10-25% in soap; may irritate the skin.

Actions: Characteristic systemic action of barium lies in its direct stimulating effect on plain muscles, regardless of innervation:

- (a) *G. I. tract:* stimulation of peristalsis, vomiting, diarrhoea, colic pain and even haemorrhage.
- (b) *C. V. system:* marked hypertension, due to arteriolar spasm, myocardial stimulation, leading ultimately to systolic cardiac arrest.
- (c) *Skeletal muscles:* tremors and paralysis of the C.N.S., in toxic doses

The fatal oral dose of soluble barium salt is 0.8 gm. and in low concentration, it depolarises the nerve fibres.

Toxicity: Poisoning may occur from mistaken selection of a soluble salt. The treatment is symptomatic and supportive. Sodium or magnesium sulphate converts barium into insoluble sulphate and the cathartic helps in its exit. I.V. calcium or magnesium as antidote for muscular

action, should be used with caution. Cardiac pain is relieved by morphine.

Uses: *Stokes-Adams syndrome* and selected cases of *heart block*. Barium has digitalis like action on the cardiac muscle but it lacks specific action, on the conduction system. The force of contraction, excitability and the rate, are increased. The degree of heart block is not altered but syncopal attacks improve and bradycardia and a systolies are prevented. Whether the action is on the idio-ventricular pacemaker or it creates a new ectopic focus in the ventricle for initiating the impulses, is not known. It is used in *doses* of 30 mg/OS t.d.s. well diluted. The dose may cautiously be increased to 50 mg/OS q.d.s. The drug is discontinued when the syncopal attack is ameliorated. However, in view of toxicity, the drug is seldom used these days.

LITHIUM

Two salts of importance are — (a) Lithium carbonate — 0.15-0.3 gm. (b) Lithium citrate — 0.3-0.6 gm.

They are remote antacids and have some action on uric acid diathesis. Lithium biurate being more soluble than Na-biurate, the excretion of urates is facilitated by the administration of lithium. However, this change takes place at a high dose level and it cannot therefore be of much value in therapeutics.

ACIDS AND NEGATIVE IONS

The important acids and their salts, used in therapeutics, possess certain common general properties, besides the special pharmacological actions of their own.

General Properties: (a) The actions of acids are mostly due to the H ion concentration; the anionic concentration giving them their individual characters.

(b) In concentrated forms, they are irritant, caustic and protoplasmic poisons, more marked with inorganic acids which dissociate more easily, precipitate proteins, dehydrate tissues and produce serious scars. In dilute forms, when used internally, they decrease the alkalinity of blood and are eliminated as acid salts by the kidneys.

(c) The organic acids are less dissociable and weaker in action. Citric acid is the weakest and lactic and trichloroacetic acids, may be used as escharotic for skin and mucous membrane.

(d) The dilute acids also act as astringent, haemostatic, sialagogue and mild antiseptic.

HYDROCHLORIC ACID AND HYDROCHLORIDES

Hydrochloric acid is a strong inorganic acid, representing 36% strength, in its pure form. Acid hydrochloric dil. — 10%—1-8 ml.

It converts pepsinogen to pepsin, enhances the duodenal secretion and is used in —

- (a) hypochlorhydria,
- (b) fermentative dyspepsia,
- (c) pernicious anaemia.

The chlorides usually have little pharmacological action and produce salt actions, mainly.

NITRIC ACID AND NITRATES

Another strong acid, used as a caustic for warts and indurated ulcers, in 10% concentration. The nitrate salts may act as diuretics, because of the renal tubular epithelium being relatively impermeable to nitrate anions. The nitrites and nitrates are also used for the management of angina pectoris and other cardiovascular disorders as already indicated in the chapter of vasodilators.

SULPHURIC ACID AND SULPHATES

A powerful irritant and corrosive Acid sulphuric dil. — 10%—3-4.0 ml., is used as a mild haemostatic and also as preventive and curative in lead poisoning, in the form of the *Imperial drink*. Sulphate ions do not readily cross the cell membranes and are used as purgatives. They also have some diuretic action.

ACETIC ACID AND ACETATES

Acetic Acid: in 5% concentration, is used as a bactericidal agent and in 1% solution, is used for surgical dressings of the skin. *Dose:* 2-4 ml.

Glacial acetic acid is rubefacient and mildly caustic. In the tissues, it is oxidised to CO_2 and combines with bicarbonates. It may give rise to acidosis, diarrhoea, diuresis and expectoration. Acetates are

primarily used as vehicles, with which, a cation is administered. Usually potassium and sodium acetates are used.

PHOSPHORUS, PHOSPHORIC ACID AND PHOSPHATES

Phosphorus: It is a solid, insoluble, luminous, wax like mass. *Dose:* 0.5–2.0 mg. Normally, it is present in bones and blood, mostly as phosphates (0.7%). Its *toxic* effects are — acute gastro-enteritis with nausea, vomiting, colic pain, tender liver, jaundice and acute hepatic necrosis. The *treatment* of acute poisoning comprises of gastric lavage with CuSO_4 — 0.25 gm/glass of water or KMNO_4 wash. The prognosis is often fatal.

Phosphoric Acid: a colourless, syrupy liquid and a refrigerant and non-irritant for digestion. It is sometimes used in phosphaturia.

Phosphates: important constituents for the metabolism of carbohydrate, lipids and proteins.

Preparations: Calcium hypophosphate	— 200–600 mg.
Calcium glycerophosphate	— 200–600 mg.
Syrup calcium hypophosphate	— 4– 16 ml.
Syrup glycerophosphate Co.	— 4– 8 ml.

Metabolism: (a) The phosphates are absorbed through the G.I. tract. The absorption is facilitated by acids and delayed by calcium, as calcium phosphate is insoluble. Its absorption and metabolism are regulated by the parathormone.

(b) After absorption, it circulates in the body as sodium phosphate, 80% being basic and 20% acid salts and about 2/3rds is excreted through urine as acid salts.

Action: The phosphates play important roles in the acid-base equilibrium of the body fluid and also in the intermediary metabolism of carbohydrate and calcium. From the inorganic phosphorus, organic phosphates like lecithin and cephalin are formed in the body, which act as nerve tonic.

Uses: (a) Hypophosphates and glycerophosphates are still used as nerve tonics in cases of wasting diseases and nervus exhaustion.

(b) Acid sodium phosphate — 1–3 gm. t.d.s., is used as an acidifier of urine.

CITRIC ACID AND CITRATES

Citric Acid. It naturally occurs in citrus fruits which are known for their Vitamin C contents and for their refreshing, alterative action. It is converted in the tissues to CO_2 and acts as a diuretic making the urine alkaline. *Dose:* 0.3–2 gm. It forms a number of salts with the alkali metals of Na, K, Ca etc. The citrate ion acts as an intermediary in the carbohydrate metabolism. With calcium, it forms a soluble complex and prevents coagulation of blood. Its sodium salt acts as an alkalinising agent and is used for the management of metabolic acidosis, which is secondary to chronic renal insufficiency or renal tubular acidosis.

TARTARIC ACID AND TARTRATES

Tartaric acid is stronger and more irritant than citric acid. *Dose:* 0.3–2 gm. It is absorbed from the gut and oxidised to CO_2 . The *Imperial Drink* contains potassium tartrate, saccharin, oil of lemon and boiling water. It acts as a diuretic and alkaliniser of urine.

LACTIC ACID AND LACTATES

Lactic Acid: It is obtained from the lactic fermentation of sugar and is also present in sour milk. *Dose:* 0.3 to 1.3 ml. It is present in blood as lactate and is excreted in urine as carbonate.

Action and Uses: (a) In pure form, it is a corrosive and is sometimes used topically for the treatment of lupus vulgaris.

(b) In 10% solution, it is used as a vaginal douche for a treatment of leucorrhoea, as a mild antiseptic.

(c) In 2% strength, it is used in contraceptive pessaries.

(d) Sour milk is an intestinal antiseptic and is used in colitis and chronic dysentery.

Sodium Lactate: It is a colourless, viscous liquid, available in 70% concentration and has many actions and uses.

It is present in Ringer's fluid and is an important alkaliniser of urine. It is useful in acidosis and is superior to NaHCO_3 as it prevents development of uncompensated alkalosis. Further, unlike sodibicarb, it stands autoclaving and when given orally, it does not irritate the stomach.

OXALIC ACID AND OXALATES

Oxalic acid is a powerful local irritant. The oxalates precipitate calcium and produce hypocalcaemia. Na or Ca oxalates act as anticoagulants.

FLUORIDES

These are present in the animal tissue, water, plants and also in bones and enamels of teeth. In bone, it is present as calcium fluoride.

It is a protoplasmic poison which inhibits enzyme action and tissue respiration and has some anticoagulant and antithyroid activities also. It is a very toxic substance producing — (a) nausea, abdominal pain, V. M. depression and convulsions, (b) Mottled enamel, giving dull and brittle teeth. The toxic dose of Na fluoride is 5 gm. Because of toxicity, it has no use, excepting as an insecticide.

CHAPTER

34

METALS, METAL ANTAGONISTS AND RADIO-ISOTOPES

HEAVY METALS, METALLOIDS AND THEIR SPECIFIC ANTIDOTES. COMMON AND DISTINCTIVE PROPERTIES. TOXICITIES AND USES. ROLE OF ISOTOPES IN CURATIVE AND EXPERIMENTAL MEDICINE

[Besides the cations and anions of the alkali metals, a number of heavy metals — arsenic, bismuth, mercury, lead and iron are used in medicine, and several others, used in industries, also produce toxicity hazards, treatable by *metal antagonists* — EDTA, Versene, Penicillamine and also BAL. Further, with advances in our knowledge of nuclear physics, it is now possible to exploit natural and prepared *isotopes*, which as tagged compounds, emit alpha, beta and gamma rays, which can be followed and measured in the body, by special counters. These new agents are being extensively used for therapeutic, diagnostic, as well as, drug metabolism studies, in the body.

The *major metals* for therapeutic uses, are — (a) *Antisypilitics* — arsenic, bismuth, mercury. (b) *Haematinics* — iron, copper, manganese and cobalt. (c) *Antileishmania* — antimony. (d) *Antringents* — lead, silver, zinc, copper and alum and (e) *Antiarthritic* — gold. The *minor metals* of tin, chromium, selenium, nickel and tellurium, are more of toxicological significance, for the prevention of industrial hazards.

The *radioactive* substances in use, are — radium, radon, phosphorus, cobalt, iodine and gold. Others like carbon¹⁴, are used in experimental studies and are known as *labelled compounds*.

Inorganic *white arsenic*, long used as Fowler's solution, a deadly poison, producing cholera like syndrome, is now effectively treated with BAL, and so also bismuth and mercury. In lead poisoning, the disodium salt of EDTA and in iron storage diseases, DTPA and TPHA are used. Penicillamine is effective in lead and mercury poisoning, and also in *Wilson's disease*, in which, the copper-binding capacity of plasma is at fault.

I¹³¹ finds its use in thyrotoxicosis, thyroid cancer and certain cardiac conditions P 32 in polycythaemia vera; Co⁶⁰ in carcinoma of oesophagus, bronchi and cervix, and Au¹⁹⁸ in pleural and peritoneal effusions, of malignant origin.]

General Properties: The heavy metals belonging to different groups of elements, possess a number of common general properties:

(a) They may act in ionic or colloidal form. The soluble salts precipitate protein and the acidic ions are the most active.

(b) The chlorides and nitrates dissociate readily and are the most corrosive, the sulphates less so and acetates, citrates and tartrates, the

least so. The double salts do not precipitate protein and are the least astringent. According to concentrations, the salts can be: *astringent*, *irritant* and *corrosive*.

(c) Most of them having slow absorption and elimination, are *cumulative poisons* and mildly *disinfectant*.

(d) The colloidal preparations have (i) Greater surface area and thus better power of penetration and less irritant action. (ii) From the colloidal state, the ionic form is liberated slowly causing more prolonged action. (iii) On injection, they produce pyrexia and leucocytosis and are sometimes used in obscure conditions like salpingitis, rheumatoid arthritis etc.

CLASSIFICATION

MAJOR METALS	<i>Antisypilitic</i> — arsenic, bismuth, mercury. <i>Haematinic</i> — iron, copper, manganese, cobalt. <i>Antileishmania agent</i> — antimony. <i>Astringent</i> — lead, silver, zinc, copper, alum. <i>Antitubercular</i> and <i>Antiarthritic agent</i> — Gold.
MINOR METALS	Tin, chromium, selenium, nickel, tellurium.
RADIOACTIVE ELEMENTS	P^{32} , CO^{60} , I^{131} , Au^{198} , $Cr.P^{3204}$, radium & radon.

ARSENIC

The preparations of arsenic are available from *two* different sources: (a) *Inorganic* and (b) *Organic*. The former, which does not have any antisypilitic action will be studied here and the latter, in the Chapter of antisypilitics.

- Preparations:** (1) *Arsenic trioxidum*: white arsenic. *Dose*: 1-5 mg.
Liq. arsenicalis — 1% Fowler's solution — 0.2 — 0.8 ml.
(2) *Arseni triiodidum* — orange yellow crystalline: *Dose*: 4-15 mg.
Donovan's solution — 0.3 — 1 ml.
(3) *Toxic compounds* for industrial and pesticidal use are — Na arsenite, Cu aceto arsenite (Parisgreen) and Pb arsenite.

Metabolism: Arsenic is absorbed easily as arsenic trioxide and deposited in the liver and kidneys. It acts as arsenious acid and is excreted through urine and faeces — slowly, about 20% in 24 hours and traces upto 4 weeks.

- Action:** (a) It is a local irritant and protoplasmic poison, which acts on the SH group of organisms and disturbs their cellular oxidation.
- (b) It is a capillary poison, which in small doses, has been associated with vasodilatation, nutrition of the skin, haemopoiesis, correction of abnormal leucopoeisis and improved general metabolism, many of which, appear to be the undeserved reputation of a traditional nature, without much scientific basis.

- Toxicity.** (a) *Acute poisoning.* It may be suicidal, homicidal or accidental. Symptoms of *acute gastroenteritis — cholera like syndrome*, with vomiting, diarrhoea, colic pain, capillary dilatation in G.I. Tract, haemorrhage, collapse and death. Kidney and liver toxicities are not uncommon. *Treatment* comprises the use of (i) Lavage, saline cathartic and demulcenta (ii) Ferri hydroxidi with Mg. oxide (iii) BAL forming stable compound of *dithioarsenate* and excreted, as detailed hereafter.
- (b) *Chronic poisoning:* This occurs in painters, starting with (i) G.I. troubles, (ii) joint pains and muscular atrophy (iii) peripheral neuritis (iv) Exfoliative dermatitis and bronzing of the skin, Vitamin B₁ deficiency is often associated with this (v) Considerable prostration, falling of hair and nails and garlic odour in the breath.

Uses: Many in the past and Fowler's solution has been mostly used:

(a) General tonic, (b) Asthma, (c) Chronic malaria, (d) Anaemia, (e) Leukaemia, (f) Hodgkin's disease, (g) Elephantiasis, (h) Psoriasis (i) Lichen planus, (j) Chronic eczema (k) Pemphigus. With the discovery of newer and better drugs, inorganic arsenic is not much used in therapeutic these days.

Prescribing hints: (a) The drug is to be given after meals and stopped when any itching of the skin or conjunctivitis starts (b) Children stand as much dose as adults (c) The drug produces a mild degree of tolerance, as in syrian peasants.

BISMUTH

Bismuth salts show paradoxes in their therapeutic scopes. Given orally

— most of the preparations act as gastrointestinal sedative, antacid and astringent. *Given parenterally* — some of them act as antisyphilitic agents, next in order after penicillin.

Preparations: (a) Bismuth carbonate, (b) Bismuth salicylate,
(c) Bismuth oxychloride, (d) Bismuth subnitrate,
(e) Bismuth subgallate, (f) Bismuth aluminate.

Dose. 0.6 — 2 gm.

Uses: *Bismuth oxychloride* is a fine powder and is used in *cosmetics* and skin troubles. (b) *Bismuth carbonate* is a sedative, protective and antacid. (c) *Bismuth salicylate* subnitrate, subgallate, are used in diarrhoea, dysentery and ulcerative colitis and the last as suppository also in piles. They are all weak antacids but more important protective and soothing agents. *Bismuth aluminate* is considered to be the best as antacid and G.I. protective. *Bismuth nitrate* is converted to nitrites by the intestinal flora.

MERCURY

A very old and problem drug, with innumerable preparations of rising and falling reputations, in quick succession.

- I. *Metallic Mercury:* Hg. cum creta—grey powder—60—300 mg.
Pil Hg. — blue pill — 60 — 300 mg.
Ung. Hg. — blue ointment — 30%
- II. *Mercuric Salts:* Hg. perchlor (corrosive sublimate) 2 — 4 mg.
Liq. Hg. perchlor — 0.1 %
Ocul. Hg. oxidi cum atropini — 0.125 %
- III. *Mercurous Salts:* Hg. subchlor — 'CALOMEL' — 30—180 mg.
Lotio nigra — (black wash), Inj. Hg. subchlor,
Ung. Hg. subchlor and also propylactic ointment containing calomel, Hg⁺⁺ oxycyanide⁺, wool fat and yellow soft paraffin, are the important preparation of calomel.
- IV. *Misc. Preparations* (i) *Inj. mersalyli* containing 200 mg. of mersalyl, 100 mg. of theophylline. *Dose:*— $\frac{1}{2}$ —2 ml.
(ii) *Mercurochrome*, dibromidihydroxy-mercuri-fluoreiscin — 2.5%, used occasionally in cases of conjunctivitis, even now.

Antisyphilitic preparations: (a) calomel ointment 33% (b) blue ointment or mercury oleate 1.3—4 gm. inunctions; (c) Injections of perchloride, biniodide and oxycyanide of mercury I.M., seldom used now.

Metabolsim: It is absorbed through all the surfaces, uniformly distributed and deposited as mercury albuminate in the body. It is excreted in urine, stool, saliva and bile. It is a cumulative poison.

Action: (a) *Externally* — it has an antiseptic and antiphlogistic action. Organic matter reduces the antiseptic action to as low as 10% only.

(b) *Internally* — it is a purgative, cholagogue and a mild diuretic.

Toxicology: *Acute:* Gastroenteritis and 'acute glomerulonephritis', needing treatment by egg albumin, lavage and the specific antidote, BAL — 5 mg/kg.

Chronic: Spongy gums, salivation, skin eruption and tremor.

Uses: Mostly discarded, excepting the following:

Externally: Perchloride, yellow oxide and merthiolate lotions; also calomel and biniodide ointments, are sometimes used for their antiseptic and antiphlogistic actions.

Internally: calomel and grey powder are used in infantile diarrhoea. Mersalyl group of preparations and Guy's pill, are used as 'cardiac diuretic'.

LEAD (PLUMBUM)

An astringent metal having some therapeutic and more toxicological importance.

Preparations: Two salts are used. (a) *Lead acetate* — sugar of lead and (b) *Lead monoxide* — letharge.

From the *former*, Lead and opium suppository, Liq. Pb. subacetatis dil or Goulard's lotion and lead lotion are prepared, while from the *latter*, lead plaster, ointment and pill, all meant for topical applications, are available.

Metabolism: Lead is very slowly absorbed. It is accumulated in the C.N.S., kidneys, liver, bone and arteries and excreted through urine, bile, sweat and foecis, as sulphide.

Action: Besides its astringent, antiphlogistic and soothing effect, the rest of its action are mostly of toxicological nature and collectively known as *Plumbism*.

- (a) Indigestion, loss of appetite, blue lines on the gums due to the deposition of lead sulphide, obstinate constipation and also typical '*lead colic*' relieved by amyl nitrite and nitroglycerine.
- (b) Anaemia with basophilic stippling of R.B.C. arteriosclerosis, granular kidneys and albuminuria.
- (c) Dysmenorrhoea, abortion, arthralgia, lead palsy, with wrist drop, from the paralysis of the extensor muscles. There may also be lead encephalopathy, amblyopia and gouty deposits.

Treatment is fairly complicated — (a) During *acute attacks*, calcium lactate and milk may be given for facilitating the deposition of lead on the bones.

- (b) *After the acute stage* is over, the patient should be delead with negative or low Ca diet.
- (c) Ammonium chloride and parathormone should be prescribed for slowly mobilising the lead into the circulation and then be excreted.
- (d) Since the discovery of EDTA, the specific antidote, detailed under metal antagonists, that is now the drug of choice for the treatment of all lead poisoning cases.

In addition to the above therapy, use of antispasmodics like atropine, papaverine and amyl nitrite for relieving pain. KI for dissolving insoluble lead compound and magnesium sulphate for helping its excretion, is also advocated.

Uses: This is mostly topical —

- (a) Lotion, ointment, suppositories and plasters are used for soothing irritation and controlling exudation, haemorrhage and inflammation.
- (b) Lead opium lotion is used for relieving sprains and
- (c) Lead calamina lotion for relieving urticaria.

ALUM OR ALUMINIUM

It is a crystalline, white mass; sweetish, astringent and soluble in water. *Aluminium hydroxide*: 0.3 — 0.6 gm., is used as an antacid. Alum is used as an astringent mouth wash and gargle and aluminium hydroxide — 0.3 — 0.6 gm., as gastric antacid.

KAOLIN

Native aluminium silicate is available in *two* varieties — (a) *Light Kaolin* — 15-30 ml. & (b) *Heavy kaolin*, from which cataplasma kaolini is made. *Neutralon*, a proprietary synthetic preparation, containing aluminium sodium silicate, is used as an important antacid.

Actions and Uses: (a) It is used as an excipient for pill masses and also as *dusting* — powder.

(b) *Cataplasma* or kaolin poultice is used for deep seated inflammations. The bandage is to be changed every 12-24 hours.

(c) It is used as a protective and adsorbent in cases of diarrhoea, dysentery and ulcerative colitis, in doses of 250/0.5 litre of water, 100-110 gm/½ hr. for 12 hours.

(d) *Osmo-kaolin*, a colloidal preparation, is sometimes used for the absorption of toxins in the intestine.

Thallium: The acetate salt is an excellent depilator in cases of ring worm of the scalp. It is used as tablets of 8 mg/kg. The hair becomes brittle in a week and falls off. It is however a very toxic substance producing vomiting, stomatitis and peripheral neuritis. *Treatment* comprises uses of stimulants, sodium iodide and sodium thiosulphate.

Chromium: An oxidising, deodorant and disinfecting agent, the *trioxide salt* is mostly used. (a) *Liq. acidi chromici* — 25%, is used for destroying warts, while (b) 2.5 — 3% lotions, are used for the treatment of ulcerated gums, foul sores and offensive perspiration of the feet.

Selenium: Chemically and pharmacologically, it is allied to sulphur. Animals feeding on selenium rich plants or meat, egg and milk, produce selenium poisoning, under the name of *alkali disease*, characterised by (i) puffy eyes, impaired vision and abdominal pain (ii) elongated hoofs and eroded bones (iii) stunted growth, impaired reproduction capacity, damaged liver, kidneys and ascitis.

Selenium is absorbed through the G.I. tract and lungs, deposited in organs and excreted through kidneys and gut. It has hardly any therapeutic use.

Nickel. A metal of no therapeutic importance but may produce annoying *dermatitis* in workers of nickel plating. Nickel carboxyl causes respiratory disturbances, capillary damage, muscle tremor and paralysis.

Cobalt: It is similar to nickel in action and may also produce primary carcinoma of lungs and polycythaemia, from stimulation of bone marrow. It is not essential for the regeneration of haemoglobin.

Tellurium: This causes gastroenteritis, muscle tremor, paralysis, respiratory arrest and convulsions. It also produces garlic breath, dry mouth, itching and anorexis.

Tin: It has limited absorption from the gut and after parenteral use, it first stimulates and then depresses the C.N.S. It also produces diarrhoea, vomiting and irritation of lungs. Stanoxyl has been used in the treatment of furunculosis, in the past.

Beryllium: It is used for preparing special grades of metal alloys of high tensile strength, in steel industry. It may cause bronchitis, dermatitis and conjunctivitis. Similarly, the vapours of *cadmium* and *vanadium*, also used in steel industry, cause respiratory and skin troubles, of the above type.

Uranium: This is used in atomic energy plant. The soluble compounds are toxic for kidneys and bones as they replace bone calcium. Death usually occurs from the kidney failure. Radium and thorium, as well as radioactive metal like uranium, produce toxic hazards for kidneys and bones. Their elimination is very slow taking several years. *Osteogenic sarcoma*, spontaneous fracture and *aplastic anaemia*, have been observed to be produced by them. They resemble lead to an extent and their metabolism and treatment also comprise similar procedures, — with uses of chelating agents, blood transfusion and DTPA and TTHA, though with inadequate success.

METAL ANTAGONISTS

Though systemic toxicity from prolonged exposures to heavy metals had long been known, hardly any effective drug of specific nature was available for therapeutic uses upto recently. This was due to the fact that our knowledge of the biochemical working at cellular level, biological antagonisms prevailing in normal physiological processes and also the nature of cell-drug interaction, as entailed in cellular and molecular pharmacology, were very little known. Advances in these aspects of study, have brought into being, increasing knowledge of the nature and mechanism of action of *trace metals* on various essen-

tial groups of thiol, SH and other enzyme systems catalysing physiological and pharmacological actions, permitting the discovery of *specific agonists* and *antagonists*, acting through diverse chemical and biochemical processes of substrate competition, competitive blockade, end-organ completion, echelation etc. It was therefore too natural that some of the *specific antidotes* for metal poisonings could come out only after this new fields of study had been undertaken.

The above work has brought into the purview of pharmaco-therapeutics *two specific groups* of metal antagonists:

1. Those acting mainly by the process of *chelation* or metal grabbing.
2. Those acting by the process of *chelation* and *enzyme protection*.

The examples of the *first groups* are — EDTA, DTPA, Penicillamine, Deferox amine and those of the *second group* — Dimercaprol (BAL or British Anti-lewisite).

These two series of *biochemical mechanisms* of drug action, have been defined and elaborated in *Chapter 4* of general pharmacology and their nature and scope of action, dealt with. As already explained, the heavy metals produce their toxic effects by combining with the reactive groups of — OH; —SH; —S-S-, —NH etc. of cellular enzymes. The antagonists are designed to compete with their legands, for preventing or reversing the toxic effects, by formation of *metal-chelate complexes*, with displacement of *hydrogen ions* from the legands and then being excreted. The chelating agents have the capacity of grafting the polyvalent metallic ions of Ca, Cu, Hg, Fe, Cr, Pb., by donating oxygen nitrogen, sulphur, forming co-ordination bonds. This results in the formation of stable, water soluble, non-ionisable ring structures, in which, the metallic ions are firmly engulfed without undergoing any precipitation. An ideal chelating agent should therefore have water solubility, resistance to metallic degradation and ability for retaining chelating activity at body fluid pH. In the present state of our knowledge, they cannot yet be considered to be exclusively specific for any one metal and are often polyvalent in action. For their therapeutic uses, high affinity alone for a metal is not sufficient but the complex has to be of low toxicity and easy excretion without damaging the excretory organs.

There are a number of natural chelating agents like-citric, malic, lactic and tartaric acids. Chlorophyll and haemoglobin are also chelated complexes. In recent years, several synthetic agents of great therapeutic possibility have been obtained and the important ones will be studied in the succeeding section.

E. D. T. A.

Ethylene diamine tetra acetic acid (E.D.T.A., Edathamil-Versene) and its Na and Ca salts (Na_2 E.D.T.A. & Ca Na_2 EDTA) have proved to possess important chelating properties for a number of heavy metals Ca, Pb, Hg, Ni, Cu, and also some other rare metals. Of these, the Na_2 salt produces a marked hypocalcemia and tetany like convulsions, on rapid I.V. injection. The *calcium disodium salt* is much less toxic and more easily maniable, producing little changes in plasma or total body calcium level. Since Ca EDTA does not affect blood calcium concentration, it is preferably used in lead poisoning.

- Actions:**
- (a) EDTA forms highly stable chelates with most of the divalent metals, which have greater affinity for it, than has calcium. Next to calcium is zinc and its excretion is greatly increased by CaNa EDTA. Other metals are — calmium, manganese, lead and vanadium.
 - (b) Although EDTA shows greater affinity for 'Ca' than Pb. in lead poisoning, due to greater availability of Pb in blood, EDTA successfully chelates lead without affecting blood calcium. Further, its calcium salt will not chelate blood calcium as is done by its sodium salt.

- Metabolism:**
- (a) CaNa EDTA is poorly absorbed from the GIT and about 80% is excreted in faeces in 24 hours. The urinary excretion of Ca is not markedly affected.
 - (b) After I.V. injection, 50% of the drug is excreted in urine, in one hour and 95% in 24 hrs, exponentially, the biological half-life, being one hour.

- Toxicity:**
- (a) Hypocalcaemia from rapid I.V. administration of NaEDTA .
 - (b) Nephrotoxicity — Lower nephron nephrosis from excretion of metal complexes and dissociation, during excretion.
 - (c) Thrombophlebitis, if I.V. injection of concentrated solution of more than 0.5% in 5% glucose is given.

Preparations: (a) Calcium disodium Edetate or Versenate — 500 mg. tab; but poor oral absorption.

- (b) Calcium Disodium Edetate injection 20% solution I.M., for diagnosis of lead poisoning.
- (c) Disodium Edetate — 20 ml. ampoule containing 3 gms of the salt, in aqueous soln. *Usual dose* — 50 mg in 500 ml of 5% glucose saline.

Uses: Both medical and industrial. It is a capital drug for a large number of metal poisonings — Pb, Hg, Ni, Cu, Cd, Ca and radium. The important uses are —

- (a) Diagnosis and therapy of lead intoxications — acute, chronic and Pb encephalopathy in children. Disodium edetate in cardiac arrhythmia.
- (b) Treatment of hypercalcaemia.
- (c) Dissolving of urinary tract calculi and removal of traces of radioactive materials.

Industrially, chelates are used as soluble metal nutrients for plants, clarifiers and stabilisers for foods and beverages and also as scale removers in boilers and water softeners.

Of these, its use in lead poisoning has been the most elaborated and satisfactory methods for the administration of the drug has been found out, using tetra-sodium salt of EDTA or VERSENE: 1 gm/30 lbs I.V. as 3% sol. in 5% glucose or isotonic saline, for 5 days, followed by a rest period of one week.

While using this agent, the possibility of toxic effects of producing hypocalcaemia and nephrosis, has to be kept in mind. Further, as they are capable of producing long range actions on the enzyme system, the possibility of disturbing this by chelates, should also be borne in mind.

D. T. P. A.

Diethylene triamine Pentaacetic acid is a polyaminoacid with greater affinity for metals than EDTA and of special use in cases of heavy metal poisonings, which do not respond to EDTA. It is used in the form of calcium chelate CaNa_3DTPA .

Metabolism: It is ineffective *orally* and is usually given I.V. 30-40% is excreted in urine in two hours, 50-70% within 4 hours and completely in 34 hours. It is a *toxic substance* and may cause nausea, vomiting, diarrhoea and kidney damage.

Dose: *Initially* — 2.5 gm I.V. infusion, followed by 4.0 gm/daily, during the succeeding days.

Uses: Its main indications are in '*iron storage*' disorders and it is also used in *idiopathic haemochromatosis* or *transfusion hemosiderosis*.

PENICILLAMINE

It is B-B-dimethycysteine, a hydrolytic degradation product of penicillin and is an effective chelator of copper, mercury, zinc and lead and promotes their excretion in the urine. It is well absorbed from the G.I. tract and also rapidly excreted in urine, not necessarily as chelates but may be even as complexes with plasma proteins. Only the D-isomer is recommended for clinical uses. Both the D & L forms, inhibit enzymes that are pyridoxal-dependent and the toxicity symptoms also resemble pyridoxine deficiencies and are improved by the administration of this vitamin.

D-Penicillamine or Cuprinine is a white, crystalline, water soluble powder, which in aqueous solution, is relatively stable at pH 2-4. It is available in *capsules* of 250 mg, 1-4 gm. per day, *orally*, in divided doses, on an empty stomach. *Potassium sulphide* — 40 mg. is also given with each meal to reduce the absorption of copper. *Its side effects are:*

- | | | |
|----------------------------|-----------------------|------------------|
| (a) Sensitivity reactions, | (b) Fever, | (c) Skin rashes, |
| (d) Leukopenia, | (e) Thrombocytopenia, | (f) Nephrosis |
| (g) Optic neuritis. | | |

Treatment: (a) Suspension of the drug. (b) Desensitisation with small doses and (c) Use of corticosteroids.

Therapeutic Uses: (a) *Wilson's disease:* or hepato-lenticular degeneration with toxic copper deposition in tissues, deficiency of ceruloplasmin or copper containing plasma protein. The condition improves with this therapy, along with the use of dimercaprol, when needed.

(b) *Lead Poisoning:* In high doses of 600 — 1500 mg.; the result is encouraging. All symptoms including colics, improve, urinary excretion of lead is enhanced and blood lead level decreases. The *oral effectivity* of the drug is an added advantage over E.D.T.A.

(c) *Mercury Poisoning:* Encouraging protective effect, experimentally.

- (d) *Cysteinurea*: and associated nephrolithiasis — established efficacy. In doses of 30 mg/kg/day, it facilitates excretion and probably acts also by the formation of 'cysteine penicillamine disulphide or 'cysteine'.

DEFEROXAMINE

It was isolated as an *iron chelate* from *streptomyces pilosus* and then obtained as metal-free legand. It has remarkable affinity for *ferric iron* but *low affinity* for calcium. This enables it to compete for the iron of *ferritin* and *haemosiderin*, while the iron of transferrin, is little affected and so also of haemoglobin and cytochrome.

Its oral absorption is only 15% making *parenteral* administration necessary in most of the cases. It is metabolised principally by plasma enzymes.

It is *used* in (a) Iron storage diseases and more particularly, in acute iron poisoning, with nearly 50% mortality. It increases urinary excretion and ameliorates the condition. (b) It is also moderately efficacious in blood transfusion siderosis but not in haemochromatosis and haemosiderosis, secondary to liver cirrhosis. (c) *Thalassaemia* — also responds to the therapy. Though originally reported to be relatively atoxic, it may produce — (i) Hypotension from histamine release after parenteral use (ii) Skin rashes, G.T. irritation (iii) Cataract.

Dose: (a) The drug is used as deferoxamine mesylate (*Deeferyl*) in amps. of 500 mg/ml. *Dose* — 8 gm. by nasogastric route in acute poisoning cases, followed by I.M. inj. — *Initially* — 1 gm — 0.5 gm/4 h. for 2 doses. The total dose should not exceed 6 gm/24 h.

- (b) In C-V collapse, I.V. route is to be used, in the same dose as for I.M. The dose should be adjusted according to urinary excretion and also the condition of the patient.

DIMERCAPROL (BAL)

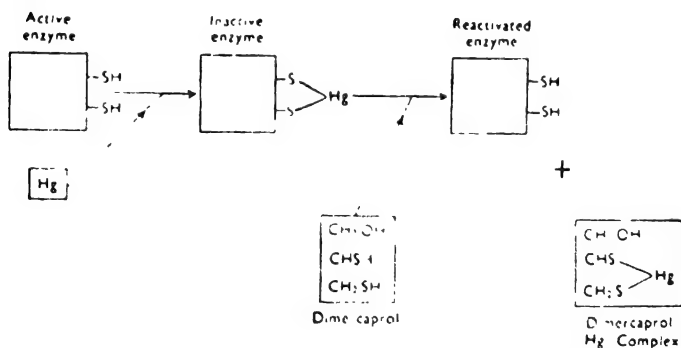
With the advent of World War II, possibility of use of arsenical war gas *Lewisite*, stimulated intensive research in the *Oxford School*, under Stocken and Thompson, for discovering an effective antidote, as a protective measure. Previous investigations on the mode of action of arsenicals had revealed the sensitivity of the SH enzyme system, to arsenicals and that glutathion and cysteine had some protective role against it. Further work on *thiol* and *dithiol* compounds were

turned to be effective products against arsenic toxicity. In this way, the drug came into use against several metallic poisonings.

British-anti-lewisite or *dimercaprol*, is a colourless oil, soluble in fat solvents and only to the extent of 6% in water. 5-10% sol. in arachis oil and benzylbenzoate, is used I.M. There is also an I.V. preparation and an ointment, but this last is irritant for the inflamed skin.

Mechanism of Action: (a) BAL forms a poorly dissociable chelate with a number of metals.

- (b) It is readily oxidised in the body and the chelated complexes can again produce toxic effects and this is a shortcoming in cases of Hg, Cd and oxophenarsan toxicity.
- (c) Excess of free-compound totally overcomes this difficulty.
- (d) It acts by protecting the SH enzyme directly by chelation of heavy metals and thereby, reactivates the free enzyme for competing with the metal, by the process of *substrate competition*.
- (e) The drug is more effective if the treatment is started early and less so, if the poison is in excess.
- (f) Dimercaprol antagonises the biological actions of As, Hg, and Cd., forming mercaptides. The enzymes involved in this process, besides SH, are catalase, anhydrase and peroxidases. It also depresses tissue respiration.



ILLUS: XVII: Mode of action of Metal Antagonist BAL

Systemic Actions: These are important and comprise principally of :

- (a) C.N.S. — Vomiting, tremor, convulsion, coma and death in toxic doses.
- (b) Hypertension due to arterial constriction. In larger doses, capillary damage.
- (c) Rise in haematocrite and lymph flow.

- (d) Peripheral circulatory failure and shock.
- (e) Metabolic disturbances in toxic doses — plasma lactic acid increased and bicarbonates decreased. Blood sugar level first rises and then falls, before death.

Toxicity: The symptoms are more alarming than serious.

- (a) Rise in systolic and diastolic B. P. with tachycardia.
- (b) G. I. irritation, headache, burning sensation and pain.
- (c) Conjunctivitis, lacrymation and tingling.
- (d) Painful sterile abscesse.
- (e) Anxiety and unrest.
- (f) In children, fever at the end of 3rd injection.
- (g) Thyroid function affected and there is decreased iodine uptake.
- (h) No teratogenicity has so far been detected.

Metabolism: (a) The drug is rapidly absorbed from the site of injection, produces peak blood level in 1/2 hour and has a short half-life.

- (b) Detoxication occurs within 4 hours.
- (c) There is rise in urinary gluconic acid and a portion is excreted as glucoromide.

Dose: (a) The drug is available for I.M. injection and also for topical administration which is painful.

- (b) The dose is calculated as 2.5 mg/kg/4 hrly. for 2 days — twice on the 3rd day and once daily thereafter for 5 days or until recovery.

Uses: The discovery of BAL as an 'anti-war gas' has been of great pharmacotherapeutic significance. It is a capital drug for *metallic poisonings* and is used in the following conditions:

- (a) Inorganic and organic arsenic poisonings, particularly *evfoliatic dermatitis*. The result is remarkable with complete healing of the skin, in about 2-3 weeks.
- (b) It is also used in mercury, bismuth, gold, zinc, tellurium, antimony, chromium and nickel poisonings, in which, it reduces the toxicity, to some extent but is useless in cadmium and antimony poisonings.
- (c) Its action in cases of lead, thallium and selenium, is more doubtful but nevertheless, should be tried with caution.

- (d) *Par se*, it is of little value in *lead poisoning* but is a good adjunct to Ca-Na EDTA, for this and to penicillamine in the treatment of *Wilson's disease*.

In passing, it is worth remembering that BAL is also the first in the series of *metal antagonists*, opening the new field of biochemico-pharmacological research, of present significance and future promises.

THERAPEUTIC SPECTRUM OF METAL ANTAGONISTS

BAL	Arsenic, mercury and gold salts. Also bismuth, chromium, nickel and copper but noneffective in lead poisoning cases.
EDTA & DISODIUM EDTA (Versene)	Calcium and lead poisoning. Also hypoparathyroidism, cardiac arrhythmia and digitalis intoxications.
DTPA, TTHA, TPHA	Iron storage disease, plutonium, radio plutonium and radiocerium poisonings.
DEFERRIOXANINE	Iron storage disorders — acute and chronic.
PENICILLAMINE OR CUPRININE	Wilson's disease, lead and mercury poisonings.

RADIOACTIVE ISOTOPES

Chemical elements have *three* essential constituents — *protons* and *neutrons* which constitute the nucleus and the *electrons* which surround the same. Protons and neutrons subscribe to the atomic weight, while electrons determine the atomic number, and hence, the chemical properties. Protons are positively charged while electrons, are negatively charged and in an atom, the number of protons and electrons is equal, so that it is electrically neutral. It is thus possible to change the atomic weight of an element by increasing the number of neutrons in the nucleus, without altering its atomic number and chemical properties.

Elements having different atomic weights but the same atomic number, are called *isotopes*. They are identical in all respects, except their mass and radioactive properties.

Nature of Radiation: In cases of a number of elements, the constitution of an atomic nucleus is such that it no longer remains stable. These

unstable elements disintegrate with the emission of various types of radiations and are therefore called *radioactive*. They may occur naturally or may be prepared artificially by the bombardment of the nucleus of a stable isotope with highly accelerated charged particles like protons or by neutrons, with the use of *cyclotron* or in an *uranium pile*.

The radiations emitted by radioactive isotopes, are termed *alpha*, *beta* and *gamma* rays. Only the gamma radiations are true rays, while the alpha and beta emissions are particulates, in nature.

(a) *Alpha particles* are helium nuclei with a relatively heavy mass. They have very little penetrating power, less than a few centimeters of air and only a fraction of millimeters of tissues.

(b) *Beta particles* are electrons and have a greater penetrating power i.e. a few millimeters of tissue.

(c) *Gamma rays* are electromagnetic radiations, similar in nature to X-rays with high penetrating power, producing little local effects.

Detection, Unitage and Half Life: Radio isotopes can be detected by a variety of methods, all of which, depend on the principle that the radiations emitted by these, produce ionisations. The methods in common use are:

- (a) Ionisation chambers.
- (b) Counters — (i) Geiger-Muller and (ii) Scintillation.
- (c) Autoradiograms for the localisation of radio active material in tissues.

Unit: The commonly used unit is the *curie*, 'millicurie' and 'microcurie'; one curie is equivalent to 3.7×10^{10} disintegrations per sec. A millicurie is the 1/1000th part of a curie (3.7×10^{13}) and a microcurie is 1/1000th of a millicurie (3.7×10^{16}).

The other units are — *Rutherford unit* — 1 million disintegrations/sec. with subunits of milli and micro Rutherford. Rad is a unit for the absorbed dose and is equivalent to an energy absorption of 100 ergs of the irradiated material.

Half-life: The loss of radioactivity is usually expressed as the half-life, which is defined as the time required for a radio isotope to decrease to 50% of its original activity. This may vary from a few seconds to 10^{12} years. The half life of some of the commonly used isotopes for clinical and experimental uses, is shown in the following table.

<i>Isotope</i>	<i>Half life</i>	<i>Isotope</i>	<i>Half life</i>
Radium ²²⁶	1620 yrs.	Iodine ¹³¹	8 days.
Radon ²²²	3.8 days.	Iodine ¹²⁵	60 days.
Cobalt ⁶⁰	5.3 yrs.	Gold ¹⁹⁸	2.7 days.
Iridium ¹⁹²	70 days.	Carbon ¹⁴	5300 yrs.
Phosphorus ³²	14.3 days.	Hydrogen ³	12.1 yrs.
Iodine ¹³⁰	12.6 hrs.	Sulphur ³⁵	7.1 days.

Biological Effects: Ionising radiations produce their effects by two mechanisms: (a) By a direct action on an organic molecule which is a constituent of the tissues. (b) By ionisation of water leading to the production and accumulation of hydrogen peroxide.

The following effects on the nucleus have been demonstrated—(i) Delay in cell division, (ii) Structural changes in chromosomes (iii) Gene mutation and (iv) Lethal effects on the nucleus, seen in the offsprings, known *dominant lethals*.

In human beings, radiations produce changes affecting the haemopoietic system, gonads, general health and local effects, like burns and development of malignant diseases. However, the effects produced by radio isotopes are fairly limited for allowing successful clinical applications and depend on their (a) distribution, (b) localisation in the body, (c) half-life storage and (d) rate of elimination.

Preparations: This is highly technical and only some general principles underlying some of the methods are outlined. Isotopes prepared, are of 2 types (a) *Pile produced* and (b) *Cyclotron produced*.

Pile produced isotopes: Most of the radioactive materials are prepared in the nuclear pile (nuclear reactor). In the reaction, the uranium fission produces a large supply of neutrons. In a critical reactor, one neutron for each uranium atom undergoing fission, is used to sustain the reaction. The remaining neutron (one and one half), used either to produce plutonium by interaction with U²³⁸ nuclei, are lost from the critical mass or are used to produce radioactive products by causing the neutrons to interact with specific substances, which have been inserted into the pile. The latter process is known as *neutron activation*.

Thus, there are *two sources* of useful radioactive substances from the pile (1) those produced as fission products and (2) those produced by neutron activation.

Both I¹³¹ and Ru¹⁰⁶ are available as fission produced isotopes. Before use, however they are to be separated and this is often difficult and costly. Therefore the majority of radioactive compounds are

prepared by the process of *neutron activation*, which may result either from the simple neutron capture or from a transmutation process. For example, radioactive phosphorus (P^{32}) can be prepared from stable phosphorus (P^{31}), by neutron capture.

Radioactive phosphorus can also be made by the transmutation if high specific activities are required. In this case, radioactive phosphorus can be separated from the unreacted sulphur by chemical procedures. Where P^{32} is made from P^{31} , such chemical separations are not practicable. Transmutation is useful for the preparation of many radioactive nuclei, specially of those of low atomic number.

Cyclotron produced isotopes: Certain radio isotopes are cyclotron produced. The cyclotron and similar particle accelerators can be used only with charged particles such as electrons, protons and deuterons. As the operation of such machines depends upon the interaction of magnetic and/or electrostatic fields. The charge of the particle undergoes acceleration and when the particles have been accelerated to a high velocity, they are caused to strike a target containing the atoms to be bombarded. Na^{21} is prepared in this way, by the interaction of high velocity deuterons with magnesium.

Sources and Scope: The sources are two — (a) *Natural* and (b) *Artificial*.

Natural Sources comprise — earth, heavy water, radium, uranium, C^{14} and K^{40} .

Artificial — these are prepared in the laboratory and used *medically* or for *experimental* metabolic and other studies.

- (a) Iodinated compounds are used in functional studies.
- (b) Co^{60} in labelled B_{12} , for its metabolic studies.
- (c) Radioactive gold, phos. and iridium, in malignancy.
- (d) Fe^{59} — for iron metabolism.
- (e) Krypton⁸⁵ and Xenon¹³³ for study of cardiac output.
- (f) Radio active sodium for study of Na concentration in E.C.F.
- (g) Strontium⁸⁵, Ca^{47} and H^3 or tritium, for other studies.

CLINICAL APPLICATIONS

I^{131}	Hyperthyroidism, heart disorders, thyroid cancer.
P^{32}	Polycythemia and leukaemia.
Co^{60}	Carcinoma of oesophagus, bronchi, radioresistant carcinoma of cervix.
Au^{198}	Pleural and peritoneal effusions from carcinoma.

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SECTION
VIII
EXCRETORY AND REPRODUCTIVE SYSTEMS

CHAPTER

35

PHARMACOLOGY OF DIURETICS

RENAL FUNCTIONS, PHYSIO-PATHOLOGY OF OEDEMAS. DIURETICS—
THEIR MODE OF ACTION AND CLINICAL STATUS

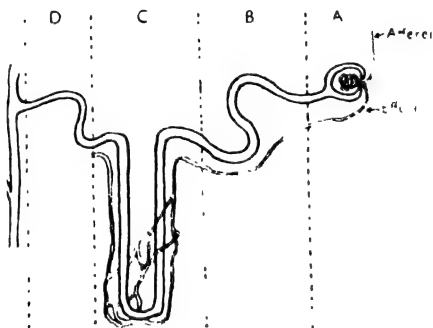
[As chief of the *excretory organs*, the kidneys function as chemical workers and not merely as mechanical filters. They excrete nitrogenous end-products and inorganic constituents not required by the body and skilfully maintain the osmotic pressure and alkali reserve of the blood. The above work is carried out through the secretion of urine, which involves glomerular filtration, tubular reabsorption and also tubular secretion, in accordance with the requirement of the body. All these have been studied by a series of clearance and other tests, which have brought into light precisely, the actual role of the various parts of the nephrons involved in the elimination of high, low and no-threshold substances, as also the mechanisms, by which, the diuretics produce their therapeutic actions in oedematous and other states, in which, the urinary secretion is reduced.

Amongst the various groups of old and new diuretics, the *neutral* and *acid-forming* salts have their own limited use, which refers to the conditions other than oedema. So also is the case with most of the *osmotically-active* substances, excepting mannitol, which has recently come into prominence in acute post-operative and barbiturate anurias and cerebral oedema. The *mercurials*, though displaced from their original position, are still called upon for use sometimes in cardiac and cirrhotic oedemas, where they may be used alone or in combination with other diuretics. *Thiazides* are now the drugs of choice in cardiac and hypertensive types of cases. The still *newer ones* like-aldosterone antagonists, ethacrynic acid and triamterine, also have similar indications. The *xanthines* and even aminophylline, have limited scopes of use these days excepting in refractory cases of oedemas, in which, they may sometimes prove beneficial, when other diuretics fail. So far as the diuretic action of *digitalis* is concerned, it occurs only in cardiac failure cases and its diuretic action, thus is not renal but *extra-renal*, in origin.

The *clinical* applications of diuretics, in actual practice, are mostly in cardiac oedema and cirrhosis, while in other kidney conditions, they are to be cautiously used or better still, avoided.]

The diuretics which increase the urinary output along with its constituents, constitute an important landmark in modern medicine, with its vast array of new drugs, acting through diverse mechanisms. Incidentally, this has also considerably changed our concepts of renal physiology and its functions. It is proposed to review the chapter in the context of these new developments.

Physiological Considerations: The functional unit of the kidney is the *nephron*, comprising, a *glomerulus* and *tubule*, each kidney having about one million such units. The glomeruli represent an area of 2 sq. meters and the tubule a length of nearly 80 kilometers. The nephron begins at a blind end, enclosing a tuft of capillaries, the glomerulus. The glomerular space or Bowmann's capsule is continuous with the lumen of the renal tubule which, structurally and functionally, is divisible into *three segments* of — (a) proximal convoluted tubule (b) loop of Henle and (c) distal convoluted tubule. The distal convoluted tubules finally empty into a series of collecting tubules, which in turn, join to form the collecting ducts. The ducts of Bellini, open into renal calyces.



ILLUSTR. XVIII: Structure of Nephron and Action of Diuretics. *A.* Glomerulus with afferent and efferent vessels. *B.* Proximal convoluted tubule. *C.* Loop of Henle and *D.* Distal convoluted tubule.

Each of these zones is charged with specific functions of filtration, general or selective reabsorption and also some secretory activity, with the unique purpose of excretion of unwanted water, electrolytes and other substances, maintaining the *milieu interieur*, in order. As a general principle, the glomeruli allow almost everything to pass and then the various parts of the tubules start exercising their discriminating role of reabsorption and secretion, detailed hereafter.

The kidneys function as *chemical workers* and not *mechanical filters*. They consume as much oxygen as the heart. About 1000 litres of blood pass through them every day and only 10% of the renal units are in a functioning state, at a time.

The glomerulus allows the filtration of water and other constituents of blood, except the proteins and colloids. Streptomycin, inulin and paraamino hippuric acid also are filtered through this. The proximal convoluted tubule allows reabsorption of glucose, most of the water, NaCl, NaHCO_3 $\frac{1}{2}$ of the urea and penicillin. The loop of Henle and the distal convoluted tubules have more selective reabsorption of needed water and certain ions, exchange of H and NaH_2PO_4 from the tubular cells for Na and K in the lumen. Penicillin and paraamino-hippuric acid are secreted through these portions.

The blood vessels entering the kidneys, are distributed as a network round the tubules. The nerve supply is from the vagus and the splanchnic sympathetic, which control the blood supply to the kidney without being concerned about the secretion of urine.

The chief functions of the kidneys are: (a) excretion of nitrogenous end-products: urea, uric acid etc. (b) excretion of inorganic constituents not required by the body. (c) maintenance of osmotic pressure and alkali reserve of the blood.

The following table gives an indication of the amount of discriminating work done by the kidneys routinely in 24 hrs.

Constituents	Filtered by glomeruli/day.	Reabsorbed tubule/day	Net excreted/day.
Water (lit)	170	168.5	1.5
NaCl (gm)	1000	985	15
NaHCO_3 (gm)	330	330	Nil
Glucose (gm)	170	170	Nil
Urea (gm)	44	14	30
Creatinin (gm)	1.7	Nil	1.7

The *kidneys* excrete mostly non-volatile waste products; the *lungs* volatile substances and the gut, heavy metals and alkaloids.

The process of urine formation is initiated in the glomerulus by the separation from the plasma, of a protein — free ultra filtrate. The volume and composition is governed by three important processes: (a) Glomerular filtration, (b) Tubular reabsorption and (c) Tubular secretion.

Glomerular Filtration: The glomerulus acts as an ultrafilter, separating from the plasma, a solution which contains all the solutes of the plasma

excepting proteins and each at a concentration identical to that in the plasma, except as modified by the absence of protein. The filtering force is the hydrostatic pressure of the blood and the opposing force is the osmotic pressure of the plasma protein. The hydrostatic pressure of the fluid is the Bowman's capsule. The *glomerular filtration* which starts the formation of urine in such a prodigal manner, is the least important aspect of the renal function. From the standpoint of pharmacotherapeutics, there is hardly any drug which can retrieve the underlying organic changes, as in heart failure, hypertension and nephritic renal failure, in which, the filtration rate is reduced. Effective treatment of the underlying conditions may improve the pathology to some extent but there is hardly any specific drug acting on the glomeruli *per se*. Those like caffeine or epinephrine have some haemodynamic actions but are not of much value. On the contrary, one can alter the rate of excretion of many substances more effectively by drugs, acting on the tubular function.

Measurement: The glomerular filtration rate and the renal plasma flow can be measured by the following tests:

- (a) *Inulin and creatinin tests:* These substances cross the glomerular membrane and are neither reabsorbed nor secreted by any of the parts of the renal tubules. Thus the amount excreted in urine over a given period, is a measure of the filtration rate. The ratio between plasma and urinary concentrations, indicates the amount of water reabsorbed from the tubules.
- (b) *Renal Plasma flow:* The amount of paraamino-hippuric acid appearing in urine in a given period, divided by the plasma concentration, is an expression of the renal plasma flow. This substance is excreted through the tubules at a low plasma concentration and is not reabsorbed by it.

Both these tests are of value in the study of the pathology of oedema, mechanisms of action of diuretics and their objectives in therapies.

Tubular Reabsorption. This is of two types — (a) *Passive* or which is due to the development of the 'concentration-gradient' in between the tubular lumen and the tubular cell. Urea is probably reabsorbed by this mechanism. (b) *Active* or in which the reabsorption of substances cannot be explained by the 'concentration-gradients' only. The process involved in the movement of such solutes is designated as active reabsorption. Special points about this mechanism are that:

(i) It requires energy which is derived from the activity of various enzymes.

(ii) There is probably a specific mechanism for the transport of each ionic species, the capacities of which are different, e.g. the SO_4 ion is reabsorbed to a limited extent but much larger quantities of the bicarbonate and the chloride can be reabsorbed.

(iii) In the proximal tubule, active transport of electrolytes takes place, leading to the development of osmotic gradient, as a result of which, water back diffuses.

(iv) In the distal tubule and the collecting duct, independent reabsorption of water or electrolytes can occur for achieving hypertonic or hypotonic urine.

(v) If one ionic species is transported by the renal tubule, it is accompanied by an equivalent amount of ion of the opposite charge, so that, independent mechanisms for the reabsorption of anions and cations, do not exist.

The substances which are actively reabsorbed by the tubules are — sodium, protein glucose, amino acids, phosphate, sulphate and water.

Proximal convoluted tubule: There is convincing evidence that sodium is actively absorbed from the tubular lumen through the tubular cell into the peritubular fluid and ultimately back into the general circulation and extra cellular fluid. By active reabsorption is meant the transport of the ion species against its electrochemical gradient, and metabolic energy is consumed in this process.

Proximal tubular epithelium is very permeable to water and quite permeable to chloride ions. Hence the reabsorption of water and the major fraction of the chloride is passive, i.e. their movement occurs downhill along the osmotic or electrochemical gradients and is secondary to the primary reabsorption of sodium. Thus reabsorption in the proximal tubule is isosmotic and water follows osmotically with the reabsorption of sodium chloride (or sodium bicarbonate); and at the end of the convoluted portion of the proximal tubule, $\frac{2}{3}$ of the glomerular filtrate has been reabsorbed with essentially no change in tubular sodium concentration or osmolarity.

However, the luminal border of the proximal tubular epithelial cell is quite impermeable to bicarbonate and other inorganic anions, such as sulphate and phosphate. Despite this, most of the filtered bicarbonate is reabsorbed. Most evidences favour an ion exchange mechanism, wherein hydrogen ions derived from carbonic acid formed by the hydration of CO_2 in the presence of carbonic anhydrase, are secreted into the tubular lumen down an electrochemical gradient

created by sodium reabsorption. In the tubular lumen, the H^+ ion reacts with HCO_3 to form H_2CO_3 , which dissociates perhaps under the influence of carbonic anhydrase in the brush border of the epithelial cell into CO_2 and H_2O . The CO_2 diffuses back into the cell, and the net result of H^+ ion secretion in exchange for sodium, is the reabsorption of $NaHCO_3$.

Little is known about the finer details of the proximal transport of the potassium. In general, evidences indicate that most or all the filtered K^+ ions are actively absorbed in the proximal tubule and also in the loop of Henle. K^+ ions finally appearing in the urine, therefore, are derived from the secretory mechanism in the more distal portions. Organic acids and organic bases are secreted actively in the proximal tubule as this is inhibited by metabolic inhibitors and competitors for the transport system.

Loop of Henle: Isotonic fluid enters the loop from the 'par recta' of the proximal tubule and a distinctly hypotonic fluid leaves the loop to enter the early distal tubule. This fluid is hypotonic, regardless of concentration of the final urine. In the descending limb, the fluid is progressively concentrated towards the hairpin turn (in large part, due to the removal of water, but possibly also due to the addition of sodium from the medullary interstitium). Most evidences indicate that in the ascending limb, sodium is actively reabsorbed (with chloride). The epithelium of the ascending limb is impermeable to water. Hence, the removal of solute without water from the tubule, represents a mechanism for urinary dilution. The sodium is transported from the lumen of the ascending limb into the medullary interstitium, whence, according to the principles of 'counter-current multiplication', involving the ascending and descending limbs of Henle's loop, there develops a stratification of sodium concentration, with the highest concentration occurring at the papillary tip.

Distal tubule and collecting duct: Sodium may be reabsorbed distally, accompanied by the permeant anion chloride, or sodium reabsorptions linked to potassium or hydrogen secretion, may occur. Much evidence has been accumulated to indicate that the distal secretion of potassium and hydrogen in exchange for sodium, involves competition between these two ion species, depending on their relative availability in the distal tubular cells.

The hydrogen ion secreted in the distal nephron may engage in *three possible buffer reactions* in the tubular lumen.

(1) In the presence of HCO_3 , it can form H_2CO_3 , which may disso-

ciate into CO_2 and H_2O and as with the proximal tubule, the net effect is the reabsorption of NaHCO_3 .

(2) H^+ ion may displace Na^+ in Na_2HPO_4 , to form NaH_2PO_4 , which is measured in the urine as titrate acid.

(3) H^+ may combine with NH_3 which is also secreted in the distal nephron to form NH_4^+ .

Reaction: (1) It is the conservative mechanism responsible for the reabsorption of filtered bicarbonate. Reactions (2) and (3) on the other hand, serve to regenerate the body buffer systems by forming HCO_3^- , over and above the quantity that was filtered.

Tubular Secretion: By this process, the electrolytes are removed from the peritubular fluid and transferred to the lumen of the tubule. Important ions secreted by the tubule are H^+ , K^+ and NH_4^+ . In addition to this, tubules can also secrete substances like phenol red, hippuric acid, penicillin, iodopyracet, salicylates, probenecid, other benzoates and many tertiary amines, all of which undergo active secretion from the tubules.

The secretion of H^+ ion is one of the most important functions of the renal tubule and it is by this mechanism that the kidney regulates the acid-base balance. H^+ is formed in the renal tubular urine. Source of the H^+ ion is the carbonic acid. ($\text{H}^+ \text{HCO}_3^-$) derived from the interaction of the H_2O and CO_2 in the presence of an enzyme carbonic anhydrase, as per equation below:

$\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ \text{HCO}_3^-$. This ' $\text{H}^+ - \text{Na}^+$ exchange' helps in many ways: (a) It facilitates the reabsorption of the bicarbonate. (b) It helps in the acidification of the urinary buffers—conversion of Na_2HPO_4 to NaH_2PO_4 . (c) It facilitates the urinary excretion of the ammonium salts.

According to Cushny, the glomeruli pass practically everything but the tubules then discriminate between the threshold and nonthreshold substances, which are as follows:

Threshold substances: glucose, water, amino acids, vitamin C, Na, K and Ca salts which are almost completely reabsorbed.

Non-threshold substances: urea, phosphates, sulphates, creatinine, uric acid, which are extensively allowed to pass.

The threshold of the kidneys to different substances is thus in proportion to the importance or otherwise, of the substance to the body economy e.g. the kidney offers no barrier to the unwanted substances

like urea and creatinine, while glucose is not allowed to pass even when the blood concentration is 100 mg%. Potassium is excreted when the blood concentration exceeds 20 mg. %, whereas sodium may be present in the blood all the same upto 300 mg%. This discrimination between the wanted (high threshold) and unwanted (low threshold), is exercised in the different parts of the tubules, the proximal reabsorbing the former and the distal reabsorbing certain substances partially and certain substances not at all, depending on their utility to the body.

All these are adjusted in a way that the *milieu interieure*, conceived and postulated by Claude Bernard, is not altered. The normal urine is hypertonic to blood; the electrolyte concentration being about twice of blood and urea about 40 times greater. For every gram of NaCl, 50 c.c. of fluid become the osmotic obligation.

The kidneys can concentrate certain substances including drugs, but not lipoids. The glomerulii filter about 125 c.c. per minute and if the extra-cellular fluid volume is calculated as 12.5 litres, the whole quantity of body fluid could be filtered out in 100 minutes. During this period 100 c.c. of urine passes into the ureters. Thus 99% of the glomerular filtrate is subjected to reabsorption. When considerable amount of electrolytes and urea are not reabsorbed by the tubules, the kidneys have to excrete more water as *osmotic obligation*. It cannot concentrate salts beyond 2% in urine.

The osmotic function of the kidneys is intimately related to the posterior pituitary and the hypothalamus, which control the water metabolism of the body. The antidiuretic hormone acts on the tubules and promotes the reabsorption of water. Cold and heat may produce variations in the excretion from 750 ml. to 15 ml. of urine/hour. The adrenocortical hormones also control the urinary output.

The reaction of the urine may range from the pH of 4.8 to 8. The acid secreted in the urine is of non-volatile nature, and if retained, would affect the alkali reserve of blood. The phosphates in the urine act as buffers, preventing acids irritating the passage. The kidneys can also produce ammonia, to neutralise any excess of acidity. Any disturbances in blood pH is reflected on the kidney function. As diuresis is an attempt to excrete any agent, in excess, in the body, any decrease of alkali or acid, is likely to disturb the pH of blood.

From their locus and nature of action, the above drugs can be considered under the following two groups:

(a) *Renal Diuretics*: acting by any of the underlying mechanisms:

(i) Increasing functioning renal units — xanthines.

CLASSIFICATION

I. Water diuretic	Water and infusions of certain plants.	III. Xanthines.	Caffeine, theobromine and theophylline
II. Osmotic and Saline	<i>Neutral salts-</i> NaCl, KCl and KNO ₃	IV. Mercurials.	Calomel, organic Hg compound mersalyl neptal, mercaptomerine, meralluride sodium chlormerodrin, mercuramide.
	<i>Alkalies, citrates and CO₂</i>	V. <i>Carbonic anhydrase inhibitors</i>	Diamox, chlorothiazide and derivatives.
	<i>Acid forming salts:</i> Ammon. chlor. CaCl ₂ <i>Ion-exchange resins</i> <i>Osmotically active molecules-urea, glucose, sucrose, mannitol, acacia.</i>	VI. <i>Aldosterone antagonists</i>	Spirolactone, amphenone.
		VII. <i>Discells. diuretics.</i>	Digitalis, thyroid, parathyroid and post. pit. extract.

(ii) Decreasing tubular reabsorption — osmotic diuretics, mercurials, carbonic anhydrase inhibitors.

(iii) Improving renal circulation — posterior pituitary extract and adrenaline.

(b) *Extra renal Diuretics*: acting by (i) improving general circulation — digitalis, (ii) increasing non-colloidal plasma constituents, such as, salts and urea.

Method of Evaluations. (a) *Heart-lung-kidney perfusion technique* of Starling and determination of rates of flow of the perfusate in drops/min. before and after the administration of different diuretics.

(b) *In vivo experiments* in rats and dogs kept in metabolism cages, with controlled water and food intake and estimation of 24 hours urinary output, before and after the administration of drug, under controlled temperature conditions. Both the volume of the urine, as well as its Na and Cl contents are determined and the effects of ST and T compared over specified periods.

(c) *Clinical tests*: as in CCF patients, using Hg diuretics as standard for comparison.

WATER DIURETICS

The kidneys maintain a constant water level in the body and any extra fluid ingested, is rejected as urine. Water thus acts as a true physiological diuretic, which action starts in $\frac{1}{2}$ hr. and may last for about 3 hrs.

According to the excellent work of Smith (1937), water metabolism is regulated by the 'antidiuretic principle' of the post-pituitary. This is inhibited and diluted after an excessive water intake, the plasma osmotic pressure falls, tissue fluids are diluted, the osmo-receptors of the internal carotid are stimulated and the impulses are sent through the hypothalamus to the post pituitary for the inhibition of ADH secretion. Tubular reabsorption is also decreased. This results in a diuretic action. Water and beer usually act as diuretics on this principle. The infusions of a number of *medicinal plants*, which are sometimes used as mild diuretics, namely *uva ursi*, *buchofolia*, *scoparia*, *juniper* and *punarnava*, act partly by their water content and partly because of the potassium and other salts and volatile oil contained in them. They are weak and harmless diuretics but ineffective in most of the conditions. *Cantharis* which acts as an irritant diuretic, is also hardly used any more.

OSMOTIC DIURETICS

They comprise — (i) *Salines*-neutral alkalies and acid forming salts, (ii) *Urea*, sugars, mannitol and acacia.

Substances most effective as osmotic diuretics must be:

- (a) Readily absorbed from the G. I. tract.
- (b) Not metabolised in the body.
- (c) Not reabsorbed by the tubules.
- (d) Produce no toxic effects, as far as possible. In practice their clinical application, excepting that of *mannitol*, is fairly restricted.

NEUTRAL SALTS OR SALINES

Sodium and potassium salts are the important members.

Sodium Chloride: In the form of isotonic and hypertonic solutions, salines are efficient diuretics removing toxins as well.

Isotonic Saline: Increases blood volume and dilutes serum protein. This results in more copious glomerular filtration, without affecting the tubular activity. The extra salt retains fluids in the kidneys as 'osmotic obligation' and this results in diuresis.

Hypertonic Saline: In this case, water is withdrawn from the cells slowly to the extra space till isotonicity is established. Thereafter, the mechanism of action is as for isotonic saline. However, due to the increased electrolyte concentration in body fluid, salt is not appreciably reabsorbed by the tubules and thus results in a prolonged diuresis.

Sodium Sulphate: Given *orally*, sodium sulphate acts as a purgative, as the SO_4 ion is poorly absorbed from the intestine. Isotonic sodium sulphate, given by I.V., drip method forces a sluggish kidney to activity. The diuretic action is due to *osmotic obligation*. After introduction of *mannitol*, its clinical use, has been greatly restricted.

In *oedemas*, both water and saline diuretics are contraindicated.

Potassium Salts: The acetate, citrate, chloride and nitrate ions are pharmacologically active. Unlike salines, these act at a lower concentration and are also alkalinisers of blood and urine, due to increased K-Na exchange, which results in the exchange of cellular hydrogen with urinary sodium ions and thus alkaline urine is formed. They also facilitate the excretion of chlorides. Potassium ion however is toxic for heart, muscle and kidney.

ALKALINISING SALTS

The carbonates, citrates and tartrates of sodium and potassium act as alkanisers of blood. They act mostly as carbonate in the body and during excretion, produce mild diuresis from osmotic obligation. They have been detailed in the chapter of alkali metals, in Chapter 32.

Acid Forming Salts: The chlorides of ammonia and calcium, produce acidosis and more important diuresis than what could be explained.

Preparations: (a) Ammonium chloride: 0.6 — 3.6 gm. (b) Calcium chloride: 0.6 — 1.8 gm.

After absorption, NH_4Cl is split into NH_3 and HCl . The former is changed to urea in the liver, leaving an excess of anion which displaces bicarbonates. Acidosis formed by CaCl_2 is due to the limited absorption of calcium from the gut, so that, an excess of chloride is absorbed which displaces bicarbonates. The resultant decrease in bicarbonates alters $\text{BHCO}_3 : \text{H}_2\text{CO}_3$ ratio, causing acidosis, which helps in the diuretic action, as follows:

(i) Sodium chloride is withdrawn from the extracellular fluid and

excreted through the urine. The excess is excreted with an equivalent amount of cation and water.

- (ii) Due to acidosis, the base-binding capacity of the tissue proteins (Donan-equilibrium), is reduced causing a movement of cellular and interstitial water to the plasma, resulting in renal excretion.
- (iii) Acidosis might also be lowering the intracellular pH of the renal tubules, inhibiting enzymatic reabsorption of Na^+ or water or both.

Toxicity: Gastric irritation and occasionally methaemoglobinaemia from ammonium nitrate.

Uses: (a) Cardiac oedema. (b) Expectorant. (c) E. coli infection.

ION EXCHANGE RESINS

These are synthetic, macromolecular, insoluble compounds, containing acidic or basic groups which undergo ionisation in aqueous solution, the actions of anions exchanging with similarly charged ions. There are three types of exchange resins available for use:

- (a) Anions, exchange,
- (b) Cation exchange.
- (c) Mixed resins.

The cation exchange resins contain acidic group, while anion exchange resins contain the basic groups. The exchange of ions is to satisfy the *Law of electroneutrality*, which means that, for every equivalent ion absorbed by an exchange resin, an equivalent of similarly charged ions, are released into the surrounding medium.

The affinity of cations differs in different cations, the order of decreasing affinity being K^+ , NH_4^+ and Na^+ . The *divalent ions* like Ca^{++} & Mg^{++} have the greatest affinity.

Exchange of ions depends on the relative concentration of a particular ion and because of the high concentration of Na^+ in the gastro-intestinal tract, in spite of its low affinity, large amounts are exchanged. At neutral or slightly alkaline pH, the resin has the maximum capacity of exchange, if the acidic group is COOH or carboxide. On the other hand, *sulphonic acid resins* are effective at a lower pH and the *phenol hydroxy* resins are active in an alkaline medium. The sulphonic acid resins have rapid action and are the most effective at acid pH values and also effective over the greater parts of the G.I. tract. The *COOH*

groups are active in neutral and alkaline pH and have prolonged actions.

During the process of the ionic exchange, NH_4 and H^+ ions are absorbed, ammonia is changed to urea in the liver and H^+ ion changes bicarbonate to CO_2 and H_2O , thus reducing the base content in the E.C.F., resulting in *acidosis*. *Chloride* ion is absorbed as HCl , producing, besides acidosis, also increased blood chloride level. The *diuretic effect* is then produced by ammonium salts, coupled with the decrease in sodium absorption. The kidneys try to compensate the acidosis in the same manner as in the case of acidifiers and strongly acid urine is secreted, containing higher concentrations of NH_4 and chlorides and diminished concentrations of sodium and potassium.

Actions: In the *G.I. tract*, because of the low pH, the COOH exchange resin exerts very little effect in the stomach, but if given as K^+ or NH_4 salts, the conversion to hydrogen cycle takes place, in the stomach.

In the *intestines*, exchange with cations takes place, the maximum exchange occurring with Na^+ & K^+ . This results in: (a) Reduction in the negative balance of Na^+ , leading to positive Na^+ balance.

- (b) Loss of K^+ and a negative K^+ balance.
- (c) Increase in the faecal excretion of Ca^{++} .
- (d) Hyperchloraemic acidosis, because of the conversion of HOO_3 to CO_2 and H_2O from the exchange of $\text{H}^+ - \text{Na}^+$.

It is because of all these that, the *mixed resins therapy* is used as that leads to less disturbances in the electrolyte balance. It comprises *carboxylic acid resin* in the *hydrogen cycle*, along with an additional resin in the *potassium cycle*. In the *stomach*, this resin is converted to the hydrogen cycle and KCl is formed, which is absorbed. This reduces the risk of potassium depletion.

Metabolism. Because of insolubility, the resins are not absorbed from the G.I. tract. However the released cations, during the process of exchange, are readily absorbed. The faecal excretion of Na^+ is increased. The passage of the resin through the G.I. tract takes a long time and it continues for several days, after the administration is discontinued.

Preparations: *Carboresin* containing 87.5% of polyacrylic carboxylic acid and 12.5% polyamine methylene resins. *Initially*, a dose of 16 gm. t.d.s. is taken in between the meals with a maximum of 24 gm. for a single dose and then the dose is adjusted to achieve the desired effect.

Side Effects: (a) Potassium depletion (b) Acidosis (c) Hypocalcaemia and tetany (d) Negative sodium balance (e) Gastric irritation — nausea, vomiting, anorexia and diarrhoea.

Potassium depletion can be prevented or minimised by potassium loaded resins, potassium being exchanged for hydrogen ions in the stomach, free potassium is then absorbed. Similarly, for preventing hypocalcaemia, calcium salts should be given and for sodium depletion, sodium chloride is to be administered.

Uses: (a) As an adjuvant, for the metabolism of oedema fluid — along with mercurial diuretics, in chronic C.C.F., cirrhosis and nephrosis.

(b) Hypertension in which destruction of Na^+ is essential.

(c) Anuric patients with hyperkalaemia, for promoting the faecal excretion of K^+ .

In practice, it is seldom used excepting for adjusting the acid-base equilibrium, by regulating the intestinal absorption. Its use is contraindicated in chronic kidney diseases, in which, acidosis cannot be compensated.

OSMOTICALLY ACTIVE NONELECTROLYTES

Urea: $\text{CO}(\text{NH}_2)_2$ is obtained from ammonium carbonate. Prismatic crystals with saline taste. *Solubility* 1 in 1. *Dose:* 1-16 gm/os in 40% solution, with orange juice, for masking its taste.

Being a low threshold substance and because of the large doses used, practically the entire quantity of urea is filtered through the glomeruli and excreted in urine with the water of osmotic obligation.

It is occasionally used in chronic nephrotic oedema without nitrogen retention. The renal efficiency test showing less than 4% concentration is an indication of renal inefficiency and a contraindication for the diuretic use of urea.

Glucose: 50-100 ml of 50% solution *I.V.* produces necessary osmotic changes for the induction of diuresis and reduction of cerebral oedema. When given *orally*, it is converted to glycogen and therefore does not produce any diuretic action.

Acacia: 6% gum saline *I.V.* restores the colloidal osmotic pressure in nephrotic oedema attracts fluid, facilitates chloride excretion and hampers tubular reabsorption. Its use in nephrotic oedema has been

completely discarded due to its renal toxicity and the clogging of kidney, as indicated elsewhere.

Mannitol: A typical hexahydric alcohol, $C_6H_8(OH)_6$, originally isolated in 1806 by Proust from plant sources and later studied by Carr and Krantz in 1933, it was found to be a precursor of glycogen in the liver.

It is absorbed from the alimentary canal, partially converted to glycogen in the liver and eliminated mostly unchanged. It is a low-threshold substance and given I.V., it is not considerably metabolised in the body. It hinders NaCl absorption, maintains isotonicity, with plasma and produces diuresis by osmotic obligation.

Its *main uses* are in — (a) Cardiac surgery and in impending renal failure cases, for which 25% solution, 50 ml is given I.V. or by drip method, side by side with glucose or saline infusions. In such cases of electrolyte depletion, the therapy has to be carried out with due precaution for ascertaining the 24 hr. of intake of fluid and output of urine.

(b) A 2.5% solution, has also been used as an irrigating fluid in transurethral resection of the prostate, because it is non haemolytic.

(c) Its other uses are in cerebral oedema, hypoxia, barbiturate anuria and also as osmotic diuretic.

XANTHINES

Caffeine, *theobromine* and *theophylline*, are the three purine diuretics. Of these, caffeine has been dealt with under analeptics, in details. Only theobromine and theophylline will be taken up here.

Theobromine: It is obtained from the seeds of *theobroma cocoa* and is not a pure alkaloid but is isomeric with *theophylline* and prepared synthetically. It is dimethyl xanthine, whereas, caffeine is trimethyl xanthine.

Preparations: Theobromine et Na salicylas or *Diuretin*. Sol. 1 in 1.
Dose: 0.6 to 1.3 gm.

Theophylline: It is obtained from the dried leaves of *Camelia sinensis*
Sol : 1 in 120.

Preparations: *Aminophyllin* or theophylline et ethylene diamine.
Dose: 0.1—0.3 gm.

Actions: Xanthines have long been used as diuretics and even now aminophylline has a large number of therapeutic uses. They act as

diuretics by *diverse mechanisms*, some of which are attributed to — (a) Glomerular stimulation, (b) Renal vasodilatation, (c) Disturbed tubular reabsorption, (d) Mobilisation of salt and water by extra renal mechanisms.

Experimental evidences from vital staining, oncometry and decrease of inulin and creatinine concentrations in tubules, are in support of this.

COMPARATIVE TABLE

<i>Xanthines.</i>	<i>C.N.S. stimulation.</i>	<i>Respiratory stimulation.</i>	<i>Muscle stimulation.</i>	<i>Coronary dilatation.</i>	<i>Diuresis.</i>	<i>Side effects.</i>	<i>Uses.</i>	<i>Contraindications.</i>
Caffeine	+++	+++	++	+	+	C.N.S. Stimulation.	Cardiac oedema and Chronic Interstitial nephritis.	Acute parenchymatous nephritis.
Theobromine	+	+	+++	++	++	Headache vomiting		
Theophylline	++	++	+	+++	+++	Gastric upset.		

Thus, of the three, *Caffeine* is no more considered as an important diuretic. *Theobromine* is reputed to produce prolonged diuresis, while *Theophylline* produces acute diuresis and is considered to be the best of the three. It also dilates the plain muscle of the coronary vessels and is useful in angina pectoris, bronchial asthma and other spasmodic conditions.

Toxicity and Uses: Most of them also have the drawbacks of producing gastric irritation and C.N.S. stimulation. Theophyllin may sometimes be considered for use in resistant cases of cardiac oedema with unimpaired renal function but never in cases of glomerulonephritis, which is a contraindication for all of them.

Aminouracils: A new *non-mercurial* oral diuretic, also named as *mictine*, it *chemically* resembles thiouracil, barbiturates and xanthines and acts by impeding tubular reabsorption. It does not inhibit succinic dehydrogenase in the tubules, like mercurials. for producing the diuretic effect. It is administered as *tablets* of 200 mg. 2-3 tab/day with food. The action is maximum in 2-3 days and ammonium chloride helps in its diuretic effect. *Aminometradine* and *Amisometradine*: are pyrimidine

derivatives, obtained by alkylating aminouracil and are effective as oral diuretics, the first being the best. They produce increased diuresis of Na and are of low toxicity. They are better than theophylline but less potent than mercurials. They act by inhibiting tubular reabsorption of Na but not through carbonic anhydrase or succinic dehydrogenase inhibition. The filtration or flow rate is not increased. *Chlorazasil*: also acts similarly and is sometimes used in hypertension. Its *side-effects* are: anorexia, nausea, vomiting and muscular weakness.

MERCURIAL DIURETICS

This is a group of potent diuretics, which if rightly used, can demonstrate dehydrating effect, but wrongly used, they show toxicity and renal damage. For their effect, the kidneys must be functionally active, as is the case in CCF, but not in hydraemic nephritis.

The salts of univalent and divalent mercury: *calomel* and *Guy's pill*, have long been in use. The *organic* preparations are of more recent origin and they have replaced the older preparations.

Preparations: (a) *Salyrgan*, containing mersalyl and theophylline 10%. **Dose:** 1/2-2 ml. I.M. or I.V.: Mersalyl and theophylline *tablets* also known as *salyrgan tablet*.

(b) *Novasural* or *Merbaphen*: a combination of Hg and barbiturates — 10% solution 1-2 ml. I.M.

(c) *Mercurhydrin* or *meralluride*: The sodium salt; 1-2 ml. I.M. It is less painful and better tolerated. The suppositories contain 600 mg. of the drug.

(d) *Neohydrine*: 18 mg. tab./1-4 tab./day. It is relatively free from toxicity.

(e) *Thiomarine sodium* or mercaptomerin produces less irritation and less toxicity to the heart. **Dose:** 130 mg./ml.; 0.5 ml. S.C.

(f) *Neptal*: 2 ml. I.M. every fourth day, preceded by ammonium chloride.

(g) *Chlormarodine*: for oral use. It has much less toxicity.

(h) *Mercuramide*: available both as tablet and I.M. injections.

Actions: The mercurials produce diuretic effect even in normal individuals and they act better in the presence of acidosis. Their action starts in 3-4 hours and lasts for about 24 hours. In large doses, they can cause acute nephritis from the liberation of ionizable mercury from the organic compounds, which varies from 30-40%.

Mechanism of actions: There are several hypotheses of which the

impediment of the tubular reabsorption mechanism is the most accepted. The older view of extra renal effect has been discarded. Unlike inorganic mercurials, the organic preparations are less damaging to the tubular epithelium. Mercurial diuresis is accompanied with *salyuresis* and the action is mostly on the proximal tubules.

Enzyme action: This is now the most accepted hypothesis on the mechanism of mercurial diuresis. These drugs penetrate the cell constituents and combine with the SH enzyme system, which is hydrolytic, as well as oxidative. About 90% inhibition is effected at 10^{-6} mol. of mercuric chloride. The organic mercurials also inhibit the succinic dehydrogenase system and A.T.Pase of kidney tissues, B.A.L. is capable of inducing a reversal of the diuretic response, which is in support of the enzymatic action of mercurials.

Potentialiation by ammonium chloride: This is fully established and largely exploited in the digitalis therapy of CCF. The mechanism of potentialiation is ill-understood. Increased Cl mobilisation and excretion as well as some other mechanisms might be involved.

Toxicity: Weakness, hyponatraemia, salivation, stomatitis, colitis and acute nephritis, all mostly due to the Hg. ions.

Choice: (a) *Mercuryhydrine* and *theomerine* appear to be the best but nothing much to choose between the two. The choice is made on the basis of potency, relative absence of toxicity and ease of mode of administration. (b) *Neohydrine* is also a good preparation and can satisfactorily be used as tablets, orally.

Uses: (a) Congestive Cardiac Failure with oedema.

(b) Pleural effusion and ascites, and

(c) May be in nephrotic oedema also.

The *routes of use* in preference are — I.V., I.M., Oral, Rectal. However, the I.V. route may sometimes be dangerous, giving ventricular fibrillation.

An *initial dose*, 0.5 ml. I.M., followed by 1 ml., the *next day*, if ineffective. If this also fails, the full doses of 2 ml. after 24 hrs. may be given. Administration of *ammon. chlor. mixture*, before and during the therapy, is advocated. An appropriate response would mean a profuse diuresis of several litres of urine, in a day or two.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase is a zinc containing enzyme, normally present in the cortex of the kidney along the luminal borders of cells, lining

the renal tubules, gastric mucosa and red blood cells. The enzyme catalyzes important reactions enabling the kidney to conserve the base, secrete acid urine and thus regulate acid-base balance of the E.C.G.



The catalysing of the reaction takes place in the tubular cells and is a source of hydrogen ions. These ions leave the cell and enter the lumen of renal tubules. During this process, the exchange of ions takes place. The hydrogen ions leaving the tubular cells, are exchanged for sodium ions present in the tubular urine and these are reabsorbed along with bicarbonate ions into the tubular cells.

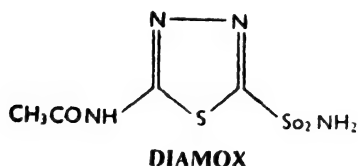
The presence of increased number of hydrogen ions in urine, reverse the direction of the reaction with formation of carbonic acid and then CO_2 and H_2O . The CO_2 enters the cell by diffusion and thus the bicarbonate ions are reabsorbed.

Along with the reabsorption of sodium, reabsorption of water also takes place for maintaining the osmotic balance between the tubular urine and the tubular cells.

Inhibition of carbonic anhydrase decreases the rate of formation of carbonic acid in tubular cells and thereby, the rate of H^+ and Na^+ exchanges is reduced. This leads to a marked increase in the excretion rate of Na^+ and K^+ and bicarbonate and a reduction in the excretion of NH_3 and titrable acids. The excretion of chlorides and phosphates is not significantly affected., which results in the diuresis of alkaline urine.

ACETAZOLAMIDE (DIAMOX)

A sulphonamide compound, represented by the following formula:



Illust. XIX : Chemical Structure of Acetazolamide

It is a specific inhibitor of carbonic anhydrase, which interferes with the production of hydrogen and bicarbonate ions restricting the

reabsorption of sodium. Sodium, thus left out, is excreted as bicarbonate and phosphate, resulting in an 'obligatory diuresis'.

Metabolism: The drug is readily absorbed from the G.I. tract and the peak plasma concentration is reached in two hours. About 80% of the drug is excreted in 12 hours and the rest in 24 hours. *Dose:* Tablets of 250 mg: 1-2 tabs/os.

Actions: (a) Besides its renal action, it produces acidosis, antiglaucoma and anticonvulsant actions, all of which, are due to the same mechanism of carbonic anhydrase inhibition, in the respective organs i.e. the brain and the ciliary body.

(b) In *large doses*, there is drowsiness, disorientation, numbness and tingling of face and extremities and occasionally, hepatic cirrhosis also.

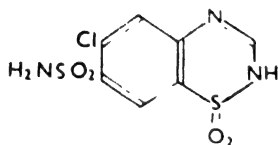
Uses: (a) Nephritis and nephrotic conditions, in which mercurial diuretics cannot be used.

(b) Combined with Hg, in cardiac oedema, refractoriness to either, can thus be avoided. Alone, its action is less rapid and dramatic than that of mercury.

(c) Treatment of epilepsy and glaucoma.

THIAZIDE AND OTHER COMPOUNDS

The first and simplest member of this group is *chlorothiazide*, having a structure as under:



CHLORTHIAZIDE

Illustr. XX. Chemical Structure of Chlorothiazide

The compound has three main properties: (i) Excretion of sodium and chloride, (ii) Excretion of potassium and bicarbonate and (iii) Inhibition of carbonic anhydrase.

As a result of these, the compound acts as a good diuretic.

S. A. R. Alternations in the chemical structure may modify the actions and produce better drugs. The free sulphonamido group at

position 7, is essential for the diuretic potency. Substitution at position 3 e.g. *benzthiazide*, also increases Na^+ and Cl^- excretion.

Compounds unsubstituted at position 3 and having double bonds between 3 and 4, though inhibiting the carbonic anhydrase more, are less effective diuretics, because of the deficiency in Na^+ and Cl^- .

CLASSIFICATION

<i>Thiazides</i>	<i>Other Compounds</i>
Chlorothiazide	
Hydrochlorothiazide	
Hydroflumethiazide	Chlorthalidone
Benzthiazide	
Bendrofluathiazide	Spironolactone
Cyclopenthiazide	Ethacrynic acid.
Polythiazide	Triamterene

Chlorothiazide: It is a stronger diuretic than diamox, acting probably by more than one mechanism — (a) carbonic anhydrase inhibition, and also (b) action on proximal tubules, not definitely settled. It increases the excretion of Na^+ and Cl^- along with K^+ and HCO_3^- and reduces the secretion of hydrogen and ammonia. The action is unaffected by acidosis or alkalosis. *Dose:* Tablets of 250 mg. 0.5—1.0 gm/day.

Toxicity: (i) Nausea, vomiting, diarrhoea, dizziness, paraesthesia and skin rashes. (ii) Hypokalaemia, hypochlorhaemic alkalosis.

Uses: (i) Control of oedema of CCF and also nephrotic oedema. (ii) Hypertension — it reduces plasma volume and sensitises the patient to the action of hypotensive drugs. It has replaced diamox, in actual therapy.

Hydrochlorothiazide: It is rapidly and completely absorbed from the gut and is 10 times more potent than chlorothiazide. *Dose:* tabs of 25 mg.; 75 mg/day.

Benzhydroflumethiazide: It is more potent than chlorothiazide. *Tabs*—2.5 and 5 mg.; *Dose:* 2.5-15 mg/day.

Trichlormethiazide: It is 5 times more potent than hydro-chlorothiazide and causes less loss of K^+ . *Dose:* 4 mg. per day.

Other derivatives in use are: *polythiazide*, and *chlorothalidone*, from the same considerations of increased potency and reduced toxicity.

Ethacrynic Acid: A potent new diuretic resembling thiazide. Its actions are independent of acid-base balance. It inhibits NaCl absorption. Its actions are very prompt and of short duration. *Dose:* 20-200 mg: Diuresis of 7 litres/day has been recorded.

ALDOSTERONE ANTAGONISTS

Aldactone: *Chemically*, a 17-spirolactone which is an aldosterone antagonist. It inhibits the tubular action of aldosterone, blocks the tubular reabsorption of sodium and secretion of potassium, resulting in increased sodium and chloride excretion and also of urine volume. Its action starts gradually and full effect is achieved in several days. *Dose:* 400 mg/day.

Use: (a) Primary aldosteronism, (b) long standing cases of cirrhosis, nephrosis and CCF, with secondary hyperaldosteronism.

Actions Summarised: The rapidly growing number of diuretics of diverse groups, has posed the need of critically analysing their status and limitations on a comparative basis. The newer diuretics are not only very potent but also because of the far-reaching biochemical changes produced by each one of them in the body causing salt depletion, *low salt syndrome* and also alterations in blood pH, they may even produce circulatory failure, coma and hypersensitivity reactions. The salient features, in respect of each of the groups, may be summarised as under:

Osmotic diuretics: The high, low and nonthreshold diuretics, practically all are gradually receding from the scene of use. The *salines* are used as alkalinisers of urine, *glucose* (50% I.V.) and *urea* (30% I.V.) in cerebral oedema, while *mannitol* (20% I.V. infusion) is given in post operative anuria, as well as barbiturate, salicylate or bromide intoxications. They all act by opposing tubular reabsorption and none is indicated in any of the general oedematous conditions.

Acidifying salts: provoke initial loss of sodium and potassium by causing an excess of chloride ions. The latter causes hyperchloraemic acidosis. Ammonium chloride is used for restoring or potentiating the action of mercurial diuretics. They are likely to cause gastric

upset and when used in patients of hepatic failure, even coma may occur.

Organic mercurials: They are still sometimes used in cardiac oedema and cirrhotic ascitis. They act on the proximal tubule by inhibiting the S-H enzymes and cause loss of sodium and chloride ions, resulting in hypochloraemic alkalosis. *Toxic effects* include ventricular fibrillation, hypersensitivity reactions, liver and kidney damage and also gastric intolerance. On prolonged use, refractoriness also may develop. They are *contraindicated* in acute nephritis and with the advent of newer orally effective diuretics, their use is becoming limited.

Xanthines: more particularly, *aminophylline*, act partly by causing an increase in the rate of the glomerular filtration and partly by decreased tubular reabsorption. They are much weaker diuretics and may cause gastrointestinal upset on oral use and hypotensive collapse, if given too rapidly by the intravenous route. They have the reputation of restoring the actions of mercurial and other diuretics in refractory patients.

Carbonic anhydrase inhibitors: These act on the distal tubules mainly, and potentiate the action of ganglion blocking amines. They are also capable of restoring the action of mercurial diuretics, improve intraocular tension in glaucoma and give relief to patients with epilepsy and chronic respiratory insufficiencies. They cause *metabolic acidosis* and are much less used these days.

Thiazides: The favourite diuretics for cardiac oedema and hypertension and are also used in diabetes insipidus. They act on proximal, as well as distal tubules and cause *hypochloraemic alkalosis*, as well as *hypokalaemia*. Hence, potassium supplementation during therapy, is essential. They produce hypersensitivity reactions, aggravation of digitalis toxicity and coma, in cases of hepatic failure.

Frusemide and ethacrynic acid: They act like the thiazides but are more potent. They are indicated in emergency pulmonary and cerebral oedemas, for reducing blood volume and also in cases of refractory oedemas. They are likely to cause allergic reaction and hepatic coma.

Triamterene: It is a less potent diuretic causing less potassium loss but increased uric acid excretion. It acts on the distal tubules and may be given to supplement the action of thiazides. The drug is likely to cause gastric irritation.

Aldosterone antagonist: It is not a diuretic as such, but exerts this action in patients suffering from hyperaldosteronism, commonly due to chronic cirrhosis or congestive cardiac failure. It acts by competing with aldosterone, in the distal tubule and preventing the reabsorption of sodium, which consequently, is excreted in excess. It can be given to supplement the action of thiazides and other diuretics. The drug

POINTS AT A GLANCE

<i>ps.</i>	<i>Mode and Site of action.</i>	<i>Indications.</i>	<i>Acid/base changes</i>	<i>Toxicity.</i>	<i>Special remarks.</i>
osmic urials.	(a) Proximal tubule. (b) SH-enzyme inhibition.	(a) Cardiac oedema. (b) Cirrhotic ascites.	Hypochloreaemic alkalosis.	(a) Ventricular fibrillation. (b) Hypersensitivity reaction. (c) Liver, GIT, Kidney.	(a) Contraindication — acute nephritis & I.V. route. (b) Tolerance formation. (c) Less used.
ozides.	Proximal and distal tubules.	(a) Cardiac oedema. (b) Hypertension. (c) Diabetes insipidus.	—do—	(a) Hypersensitivity. (b) Enhanced digitalis toxicity.(c) Coma in hepatic failure.	(a) Maximum hypokalaemia. (b) Potassium supplement essential.
oside & acrynic acid	As above.	(a) Emergency circular & pulmonary oedemas. (b) Refractory oedema. (c) Reduction of blood volume	—do—	(a) Circulatory failure. (b) Hypersensitivity reaction.	Very potent.
ameterine.	Distal tubules.	As thiazide supplement.	—	G.I.T. disturbances.	(a) Weak action, (b) Unlike thiazide, less potassium but increased uric acid excretion.
rbonic hydrase ibitors	(a) Distal tubules (b) Carbonic anhydrase inhibition.	(a) Restoration of Hg. action. (b) Glaucoma (c) Epilepsy (d) Chr. Respir. insufficiency.	Metabolic acidosis. ...	(a) Hypersensitivity (b) Neurological ...(c) Coma in hepatic failure.	Potentiation of ganglion blocking amines.

lyng salts.	Na & K loss, neutralisation chloride ions.	Restoration of Hg. action.	Hyperchloraemic acidosis.	GIT disturbances, Coma in hepatic failure.	Alternative to Diamox for restoring Hg. diuresis.
themas.	(a) Increased glomerular filtration. (b) Decreased tubular reabsorption.	(a) Restoration of Hg. action (b) All refractory oedemas.	—	(a) GIT disturbances. (b) Collapse from rapid I.V. use.	Weak action.
Threshold.	Renal reabsorpt. cap. exceeded.	(a) Salines for rendering urine alkaline. (b) Glucose 50% I.V. in cerebral oedema.	—	—	Not useful in oedema.
Low threshhold.	Mostly rejected by tubules.	Urea 30% I.V. in cerebral oedema.	—	G.I.T. upset.	Seldom used.
Nonthreshold.	Completely rejected.	Mannitol — 10% in saline base, IV drip in post-operative & barbiturate anaesthesia.	—	Increase blood vol.	C.I. in heart diseases.
oestosterone agonists.	Competitive inhibitors of distal tubules.	(a) Thiazide supplement (b) Refractory oedema (c) With other potent diuretics	Hyperkalaemia.	(a) CNS depression (b) Hypersensitivity.	Weak action, in deficiency cases mostly.

salt syndrome is produced by all potent diuretics — Hg. thiazides, urosemeide and ethacrynic acid.

however, is liable to cause CNS depression and hypersensitivity reactions.

THERAPEUTIC CONSIDERATIONS

The indications of the use of diuretics are many but in actual practice, uses are extremely few. *Therapeutically*, they are indicated in suppressed or depressed urinary output, which may be due to (a) causes pertaining to the kidney, such as nephritis, (b) causes not pertaining to the kidney e.g. C.C.F., cirrhosis and hypertension.

Though the diuretics are used in conditions other than oedemas also, in most of the conditions, the latter is a natural accompaniment, the drainage of which, is the primary objective of the diuretic therapy. An understanding of the pathological physiology of this condition is therefore necessary for proper selection and rational use of these agents, in oedemas.

Pathogenesis: The normal volume and composition of the extracellular fluid (ECF) are governed by a series of complex mechanisms, for which, the intake of fluid and electrolytes from the G.I. tract and their excretion by the kidneys, have to be sensitively adjusted by a number of factors—cardiovascular, renal, hormonal and metabolic, which all have to play their distinctive roles for maintaining the homeostasis. In oedema, the volume as well as composition of the ECF are altered and there is accumulation of more water and electrolytes in the ECF. This may be from high intake, low excretion or from excessive parenteral fluid therapy. The decreased renal excretion again may be of different origin—cardiac, hepatic and renal. The relationship between intestinal absorption and circulating plasma, depends upon a dynamic equilibrium, across the capillary membrane and involves pressure within the blood vessels and osmotic activity of the plasma proteins. In *cardiac oedema*, it may be circulatory inefficiency; in *cirrhosis*, disturbances in portal circulation and pressure and in *nephrosis*, hypoproteinaemia, but in all these conditions, besides the disturbances in the equilibrium of the capillary membranes, the common and the most important denominator in the decreased renal excretion, both from glomerular filtration as well from tubules, is the reabsorption mechanism. There is retention of sodium chloride and bicarbonates and osmolarity changes in the ECF. The role of aldosterone in the above regulation is also disturbed. *In substance*, there is, not only ECF changes from the lowered rate of excretion but also a decrease in the osmotic pressure of the circulating blood and probably,

an excess of steroid secretion endogenously or from exogenous administration.

The oedematous condition is accompanied by decreased urinary output, oliguria and even anuria, with concomitant retention of electrolytes and water. The therapeutic goal in this condition, therefore is:

- (a) Restoration of the normal action of the heart.
- (b) Assisting the kidneys to facilitate excretion of water and electrolytes by suppressing their reabsorption with the help of drugs, and
- (c) Reduction of the salt load by the intake of low salt diet. Specific management however varies from one particular condition to another.

Cardiac Oedema: It occurs primarily in cardiac decompensation and its therapy, which has already been indicated in Chapter 28, comprises:

- (a) Adequate digitalisation, (b) use of diuretics — (i) mercurial diuretics for rapid mobilisation of the oedema fluid and (ii) thiazides for the maintenance of oedema free state.

It is needless to go into the controversy of relative status of digitalis and its adjuvant diuretics and also to reason whether the primary beneficial effects are exerted through the heart or the kidneys. There is unanimity of views that the diuretics play their important role, by assisting the decompensated heart to do its work better, by relieving it from the excessive fluid load. Consequently, the patients also feel much relieved. It now appears that it may not be essential to cause acidosis in every case of mercurial diuretic therapy and further the place of mercurials is gradually being taken away by the newer orally effective diuretics.

Ascites: The condition is usually of hepatic origin, from cirrhosis. Due to the hepatic damage, there is portal obstruction and hypertension. The ascitic fluid collecting in the peritoneal cavity, may have to be periodically drained by paracentesis. However, the concomitant administration of mercurial diuretics, reduce the frequency of paracentesis and for patients refractory to the above, other diuretics may be tried. The use of thiazides may be dangerous, because they, by causing depletion of potassium, may land the patient into hepatic failure. Patients of cirrhosis frequently go into secondary hyperaldosteronism,

a condition which tends to favour the fluid retention. This tendency can be countered by giving aldosterone inhibitors like *aldactone*.

Renal Oedema. This may be associated with a number of conditions of diverse etiology, (a) acute glomerulo nephritis, (b) acute tubular necrosis, (c) chronic nephritis, (d) Type II nephritis and nephrotic syndrome. They eventually lead to the renal failure which may also occur from other causes like severe burns, gastrointestinal haemorrhages, severe infantile diarrhoea, renal infarction etc.

In most of these conditions, there is oedema, oliguria or anuria, electrolyte imbalance, nitrogen retention and eventual kidney failure.

(a) *Acute nephritis*: is often due to streptococcal infection affecting children and adolescents and is characterised by pain, fever, oedema of face, scanty high coloured urine containing blood. Its management involves the use of penicillin, fluid and salt restriction in accordance with the fluid and electrolyte output, per day, and a very conservative expectant treatment, with diuretics, if at all to be used. Mercurials and potassium salts are definitely contraindicated.

(b) *Acute tubular necrosis*: is often due to heavy metal poisoning like mercury, with characteristic suppression of urinary secretion. The treatment is again expectant and diuretics generally have no place, excepting probably the careful use of mannitol and also the chelating agents.

(c) *Chronic nephritis*: usually occurs at the terminal stage and the use of any diuretic is usually contraindicated, because of the risk of further damaging the already damaged kidney.

(d) *Type II nephritis and nephrotic syndrome*: The therapy is based on the (i) Correction of hypoproteinaemia, (ii) Use of thiazides and aldosterone antagonists, (iii) Use of prednisolone and other immuno suppressive hormones, as well as mannitol diuretic, (iv) Mercurials and even urea, are undependable and may sometimes be dangerous for the kidneys.

The type of fluid to be given, in all these cases, would depend on the biochemical condition of the body fluid. (a) If potassium is increased, large quantity of glucose combined with insulin may be given. (b) If acidosis is present, sodium acetate and bicarbonate should be given. In cases of hyperkalaemia. (c) Ion exchange resins, 50 gm orally would increase potassium excretion, besides acting as a diuretic, Mannitol I.V., slow drip 20% sol., 200 cc. for 2 to 3 days, may set in the diuresis, after which, depending upon the level of K and Na, potassium chloride 1-2 gm orally or Cal. gluconate 10% 10 c.c. I.V., may be given, if the levels are low.

If none of these works and the anuria persists, recourse to peritoneal dialysis, artificial kidney and haemodialysis, should be resorted to, the underlying principle is to dialyse the patient's blood across the semipermeable membrane to remove the extra water and crystalloids but not the colloids, thus improving the blood chemistry of the patient.

Cerebral Oedema: In this, hypertonic glucose, sorbitol, mannitol and urea are generally used. Further, as general measures, rest to the kidneys, treatment of infection, appropriate protein, fluid and electrolyte administration, glucose, fruit juices and saline purges are indicated.

Complications of Diuretic Therapy: These are several, well understood now and preventable. They usually occur from:

- (a) Too rapid mobilisation of oedema fluid causing malaise and asthenia.
- (b) Excessive depletion of extracellular sodium chloride producing cramps.
- (c) Excessive depletion of potassium particularly after thiazides, increasing digitalis toxicity and enhancing hepatic failure in cases of cirrhosis.
- (d) And also alkalosis caused by mercurials and chloruresis caused by ethacrynic acid, both of which, can be prevented by the use of ammonium chloride.

For potassium depletion, dietary potassium is generally adequate. Enteric coated potassium chloride combined with diuretics, should usually be avoided as they are undependable. Potassium salts are contraindicated in the therapy of triamterene and aldosterone antagonists:

Refractory Oedema: This is often due to the indiscriminate use of potent diuretics and may also be associated with the following:

(a) Hyponatremia, (b) Metabolic alkalosis after mercurial diuretics, (c) Acidosis from acetazolamide, (d) Decreased glomerular filtration rate due to hypovolaemia and (e) A natural decrease in diuresis due to diminution in the amount of oedema fluid available for mobilisation, after prolonged uses of diuretics.

Combination Therapy. The use of more than one diuretic, at a time, is sometimes necessary. It is better to initially select an appropriate

drug and administer it according to recommended dosage schedule and then switch over to another, from time to time, so as to prevent the refractoriness. All diuretics are potentially toxic and should never be used in those conditions, in which, they are contraindicated. The reaction of the patient to the drug, should also be taken into account. Diuretics should, if at all necessary, be combined in such a manner, as to potentiate each other's action: (i) Aldosterone antagonists and thiazides, (ii) Mercurials and ammonium chloride and (iii) Threophylline along with other diuretics, in refractory cases.

CHAPTER

36

PHARMACOLOGY OF THE REPRODUCTIVE SYSTEM AND ACCESSORY ORGANS

PHYSIO-PHARMACOLOGICAL CONSIDERATIONS OF UTERUS. OXYTICS, ABORTIFACIENTS, UTERINE SEDATIVES AND DRUGS ACTING ON THE MAMMARY GLANDS

[The female reproductive organs undergo considerable duress during the reproductive period of a woman and are endowed with great reserve powers. The non-parous uterus weighs 50 gms. and has a capacity of 5 ml only, while, at full term of pregnancy, its weight and capacity increase 20 and 1000 folds.

The drugs acting on the reproductive system are — (a) Oxytics and abortifacients. (b) Uterine sedatives and haemostatics and (c) galacto and antigalactagogue agents.

The *oxytics* comprise posterior pituitary extract and ergot. Besides oxytocin and vasopressin, the gland also elaborates and stores ADH, concerned with water metabolism and urinary excretions.

Oxytocin is a plain muscle stimulant including uterus. It produces rhythmic contractions and relaxations from fundus to cervix, as occurring during delivery, leading to expulsion of foetus. It is used in the second stage of labour with uterine inertia after full dilatation of the os. It is also used in diabetes insipidus.

Ergot is an infected rye containing a series of alkaloids, of which ergometrine, ergotamine and ergotoxine are endowed with pharmacological activities. Of these, ergotoxine and ergotamine possess sympatholytic effects and used in migraine, while *ergometrine* is used in delivery, in the third stage and better still after the delivery of the foetus, for expelling the placenta, stop post-partum haemorrhage and involute the uterus.

Oxytocin, *oestrogen*, quinine, ergot, oil of savin and heavy metals, have been tried as *abortifacient agents*, with undependable results and toxic effects.

Hydrastis, *viburnum*, *progesterone*, *vitamin E* and *laudanum* are believed to possess some uterine sedative action in threatened or habitual abortion cases but here again, their uncertain efficacy as *uterine sedative*, limits their uses.

Prolactin, milk, sago, barley and porridge are believed to increase secretion and flow of milk in nursing mothers, acting as *galactogogues*, while, testosterone and belladonna alkaloids reduce or arrest the same and are used as *antigalactogogues*, sometimes, in cases of milk fever in parturient mothers.

A number of drugs — alcohols, bromides, iodides, anthracenes, sulphonamides, belladonna and arsenic are excreted in mother's milk and this point is to be borne in mind in cases of breast-fed babies while treating the nursing mothers with any of these drugs.]

Physiology: As a primary organ for conception the uterus has to undergo considerable duresses throughout the major part of its existence. Further, the endocrine control through the pituitary and ovary and the changes undergone by it at different phases of life, submit it to very heavy demands for frequent adjustments.

The myometrium consists of an inner circular and an outer longitudinal layer of musculature. It shows rhythmic contractions, starting from the fallopian tubes and passing on to the uterus. These contractions resemble peristaltic movements and are increased during menstruation and the latter part of pregnancy. When the circular fibres contract, the other relax and *vice versa*. Similarly, when the fundus of the uterus contracts during delivery, the cervix opens, facilitating expulsion of the foetus.

The myometrium is supplied with sympathetic nerves which also contain cholinergic fibres. The sympathetic is motor for the circular fibres of myometrium and longitudinal fibres of the cervix. It is relaxant for the longitudinal fibres of corpus uteri and the circular fibres of the cervix. The human uterus is contracted by pilocarpine and relaxed by atropine.

The non-parous uterus weigh about 50 gm. and has a capacity of 5 ml. only, which during pregnancy, goes upto 1 kg. and 5 litres respectively.

The role of anterior pituitary hormones on the development and functioning of the ovary through the follicle stimulating hormone (FSH) and the luteinising hormone (L.H.) will be discussed in the chapter of female sex hormones. The action of the posterior pituitary hormone through oxytocin and vasopressin, the pressor-antidiuretic principle, on the uterus, renal excretion and water metabolism, will be studied in this chapter.

Pharmacology: Many drugs act directly or indirectly on the female genitalia and accessory organs. They are conveniently classified as:

- (a) Oxytocics and abortifacient drugs.
- (b) Uterine sedatives and haemostatic agents.
- (c) Galactagogue and antigalactogue drugs.

OXYTIC DRUGS

These drugs increase uterine contraction, expel the foetus and placenta during delivery, check post-partum haemorrhages and help in the involution of the uterus.

They are also sometimes called *ecbolics*. The drugs which increase the flow of menstrual blood, are known as *emmanogogues* and those which evoke abortion before the foetus is viable, are known as *abortifacients*. There is however, unity in the mechanism of actions of these different groups of drugs.

Though the uterus is supplied by the cholinergic and adrenergic nerves, in the case of human uterus, these considerations are of very little significance. The oxytocic drugs act primarily, directly on the plain muscle of the uterus.

Two important drugs, which are to be considered in this chapter, are: (a) Posterior pituitary extract and (b) Ergot alkaloids.

POSTERIOR PITUITARY EXTRACT

The posterior lobe of the pituitary gland is minced, defatted with acetone, dried into powder, extracted with glacial acetic acid 0.25%, filtered, assayed and ampouled. This constitutes a total extract, containing different fractions of the posterior pituitary body as it serves as a store for the hormones secreted by the hypothalamus, besides its own.

- (a) An oxytocic principle — *oxytocin*.
- (b) A pressor — antidiuretic principle — *vasopressin*.

Anti Diuretic Hormone (A.D.H.). The neurones of the hypothalamic supraoptic nuclei elaborate peculiar colloid like granules which migrate in or along the exoplasm of the supraoptic and related neurones down the stalk, into the posterior lobe where they are stored as posterior lobe hormones. The release of these stored neurosecretion is controlled by the hypothalamic neurones, in which, the secretion is elaborated.

These active principles are *polypeptides* with a molecular weight of about 1000 and are present in the neurohypophysis, in combination with a protein neurophysin, which serves as a carrier during the transport and storage of the hormone.

Each of these peptides is composed of eight amino acids, of which, six are common to all. Tyrosine, cystine, leucine, isoleucine arginine, phenylalanine and lysine are some of the important amino acids present in different groupings, in these hormones. From the work of Duvigneau and Vandýke, further fractionation of A.D.H. and vasopressin, has partially been possible.

A specific control on the rate of secretion of A.D.H. is exercised

by the osmotic pressure of the plasma. Specific receptors called *osmo-receptors*, situated in or near the nuclei, are excited even by slight elevation of the osmotic pressure, causing release of A.D.H. A fall in the osmotic pressure of plasma, produces an opposite effect. The volume of the circulating fluid, also modifies the rate of liberation of A.D.H. independent of changes in the osmotic pressure. Expansion of the volume reduces while contraction leads to an increased secretion of A.D.H.

The hypothalamic nuclei secreting the A.D.H., have direct or indirect synaptic connections with an unknown number of centres in the C.N.S. Thus the rate of release of the hormone can be accelerated or diminished by the remotest activity in the C.N.S., leading to the excitation or inhibition of the controlling hypothalamic nuclei e.g. excitation and antidiuresis, are evoked by pain or emotion and inhibition and diuresis, are provoked by cold environment. Haemorrhage has been a powerful accelerator of the release of ADH, as also the *Low salt syndrome*, after uses of diuretics in hypertension.

So far as its distinctive actions are concerned, it increases the rate of reabsorption of water without modifying the rate of glomerular filtration, by facilitating passive reabsorption of water in the distal convoluted tubules. This effect occurs in three stages — (i) An initial anuria, due to ureterial spasm (ii) A brief diuresis due to the rise in B. P. and renal vasodilation and (iii) An oliguria, due to increased tubular reabsorption of water. Only in larger doses, it causes direct vasoconstriction, rise in B. P. and also some stimulation of the smooth muscles of the intestine and the uterus.

Vasopressin: It shares several properties of oxytocin but it is a more potent antidiuretic and pressor agent, constricting the coronary vessels also. Its oxytocic and galactogogal actions, however, are inferior.

It has been suggested that oxytocin helps in the movement of seminal fluid up the uterus to the fallopian tubes and at full term, also aids parturition, though this view has not been fully substantiated.

Oxytocin-induced contractions of the isolated uterus are not antagonised by atropine, antihistaminics and L.S.D., but by sodium thio-glycocholate, which latter, by reducing the S-S linkage in the oxytocin molecule, prevents the contractile reform.

Oxytocin: This is the principle which is responsible for (a) contraction of smooth muscle of the uterus and also (b) contraction of myoepithelial cells of the breast. It initiates, maintains and later, brings about 'milk ejection or 'let down', by the contraction of lactiferous ductules.

Oxytocin is liberated reflexly from the posterior pituitary gland into the blood stream. Unlike vasopressin, oxytocin lowers the B.P. and dilates the coronary arteries. It is not an antidiuretic.

Total Extract. This combines the effects of all the principles.

Actions: *Plain muscles:* There is marked stimulation of the uterus in guinea pigs, at all stages, while in rabbits and human beings, there is little action during the earlier stages of pregnancy but more effect during the end of the pregnancy and during labour. Human uterus is sensitive to these effects during menses but the cervix is not. The contraction induced by the posterior pituitary extract, resembles normal labour contractions. The effects of the posterior pituitary extract on the plain muscles of the intestine, are inconstant stimulations.

C. V. System: There is a prolonged B. P. rise, with constriction of the coronary and cerebral vessels but dilatation of the renal vessels.

Other effects: There is a short diuresis, followed by prolonged antidiuresis and there is anti-insulin action on the metabolism. Folliculin and thyroxine act synergistically to the posterior pituitary extract while progesterone acts antagonistically to it.

Preparations: (a) Dry powder — 0.5 mg representing 1 unit of oxytocic activity. Liquid extract — 10 units/ml. *Dose:* 0.5-1 ml. S. C.

(b) Pitressin or vasopressin injection — containing 20 (pressor) and not more than 14 oxytocic units/ml.

(c) Vasopressin tannate, a water insoluble suspension in oil-containing 5 pressor units and not more than 0.25 oxytocic units/ml.

Assay. It differs with the two principles.

For oxytocin, the following methods of study, in comparison with the international standard:

- (a) Depression of chicken blood pressure
- (b) Stimulation of rat uterus and
- (c) Stimulation of virgin guinea pig uterus.

For vasopressin, the rat and cat B. P. rise methods are used.

Toxicity: (a) Water retention and even water intoxication.

(b) Pallor, nausea, vomiting, abdominal cramps.

(c) Spasms of the coronary vessels which may be dangerous in patients with coronary insufficiencies.

Uses: These would somewhat vary according to the hormone considered. Oxytocin would specially be indicated for the *induction of labour* and vasopressin for the palliative therapy in *diabetes insipidus*.

The other uses of a posterior pituitary extract, besides the above, are:

- (a) *Induction of abortion* after preparation of the patient with oestrogen — 5 mg. or stilbaesterol — 3 ml/day, for 7 days. The result is undependable.
- (b) Shock, collapse and hypotensive stages.
- (c) Post operative tympanites.
- (d) Herpes zoster.

ERGOT

Ergot or *Secale cornutum*, is an infected rye, in which the ovary is attacked by the fungus, *Claviceps purpurea*, filled with mycelium, the proteins being broken down into a series of aminoacid derivatives, to which, all the actions of ergot, are due.

Ergot is straight or arcuate; 1.5 — 4 cm. long, fusiform, longitudinally furrowed, transversely cracked, brittle, dark violet, black, odour and taste-characteristic. Its actions are mostly due to its *alkaloids*, grouped as under:

Pharmacologically active <i>l</i> -rotatory		Pharmacologically inactive <i>d</i> -rotatory	
Water insoluble	Water soluble	Water insoluble	Water soluble
Ergotoxine			
Ergotamine	Ergometrine	Ergotinine	
Ergocristine		Ergotaminine	Ergometrinine
<i>Amines</i> — Tyramine, histamine		<i>Sterol</i> —	Ergosterol, fungisterol.
<i>Bases</i> — Choline, acetylcholine			Fixed oils.

Of these, only ergometrine and ergotamine are of therapeutic importance, while ergotoxine is used as a pharmacological tool for eliciting nature of sympathetic activities of drugs.

Preparations:	(a) Prepared ergot	0.15—0.5 gm
	(b) Liq. Ext.	0.60 —1.2 ml.
	(c) Ergometrine malleate	0.5 —1.0 mg/os
		0.25 —0.5 mg I.M.
		0.125—0.25mg I.V.
	(d) Ergotamine tartrate	1.0 —2.0 mg/os

- Historical:* (a) Ergot has been in therapeutic use as 'Assyrian tablet' or 'womb remedy', since 600 B.C.
- (b) In the middle ages, its toxic properties were known and the 'gangrenous legs', described as 'consumed by the Holy fire and blackened like charcoal'.
- (c) Its alkaloids were recognised mostly in this century by the work of Barger, Stoll and Dudley.
- (d) There have been epidemics of ergot poisoning in Russia and Ireland, even in this century.

Ergotoxine and Ergotamine: Absorption is irregular from the G.I. tract but more satisfactory after I. M. injection.

C.N.S.: Variable action and a mixture of stimulation and depression.

Sympathetic nervous system: (a) Often stimulation from therapeutic doses and depression or paralysis from higher doses. (b) Adrenergic nerve impulses are blocked and V. M. Reversal of Dale produced.

C. V. System: (a) Vasomotor stimulation and B. P. rise. Inotropic and chronotropic responses of the heart to the sympathetic stimulation are not observed. (b) Capillary endothelium is damaged and because of the out-pouring glairy secretions, thrombosis and gangrene are produced.

Uterus: (a) In small doses, the automatic contractions are increased while with larger doses, the tone is raised and spasms occur. (b) Even immature uterus responds to the drug but gravid uterus is much more sensitive. (c) The action may be due to direct muscle stimulation. Ergotamine and gynergine (lysergic acid derivatives), possess similar but more specific actions in migraine.

Ergometrine or Ergonovine: It is also a lysergic acid derivative. The malleate salt is yellowish, microcrystalline, with a solubility of 1 in 36, which is not the case with the other group of ergot alkaloids.

Action: *Uterus:* a prompt and powerful contraction after I.V., I.M. or oral use. The contraction is firm and spasmodic, with blanching of the muscle. Even isolated rabbit uterus which is not stimulated by ergotoxine, is stimulated by ergonovine. The tonus also is increased. Uterine action is produced in 10^{-6} concentration. Guinea-pig uterus is more sensitive to its action, which is potentiated by oestrone.

Circulation and respiration: No significant effect on the B.P. but with large doses, there is a fall. The heart, respiratory rate and the stroke volume are depressed. It produces mild cyanosis but no gangrene of the 'cook's comb'. It is $\frac{1}{4}$ as toxic as ergotoxine.

Other smooth muscles: There is pupillary dilatation, constriction of leg vessels. The intestine is relaxed and BMR increased like adrenaline.

Most of the actions thus simulate adrenaline and the uteine action may be both sympathomimetic and direct musculotropic.

Fluid Extract: It combines actions of both, but being unstable, is seldom used.

Toxicology: Acute: It may occur from the abuse of the drug as an abortifacient — (i) G. I. irritation, (ii) Tingling and itching of the skin, (iii) Uterine haemorrhage, followed by abortion.

Chronic: It sometimes occur in epidemic forms from the use of the infected rye. A neurotoxine with vitamin A deficiency, may subscribe to it. It is usually found in two forms:

- (i) *Gangrenous form:* The extremities are mostly involved and there is damage of the endothelium, glairy secretion and thickening of the vessels. It differs from pellagra and Raynaud's disease.
- (ii) *Spasmodic form:* (a) There is itching, tingling and formication. (b) The sensory troubles are followed by motor disturbances, sometimes muscular spasm, staggering gait, vomiting, diarrhoea; diminished sight and hearing and epileptiform convulsions. It is different from lathyrism.

COMPARATIVE TABLE

Drug	Absorption	Toxicity	Blood vessels	Uterus	Other actions
Ergotoxine and Ergotamine	Delayed and irregular	+++	Vasoconstriction, cyanosis and gangrene.	(a) Rabbit uterus depressed. (b) G. pig uterus- tonic contraction	(a) Antiadrenaline action. (b) Blood sugar unaffected. (c) Pupillary constriction
Ergometrine	Rapid from all routes.	Less	(a) Uncertain B.P. effect. (b) Mild cyanosis but no gangrene.	(a) Isolated rabbit uterus (b) Action prompt.	(a) No antiadrenaline action (b) Blood sugar raised. (c) Pupil dilated.

PHARMACOLOGIC RESPONSES OF PLAIN MUSCLE TO DIFFERENT GROUPS OF DRUGS

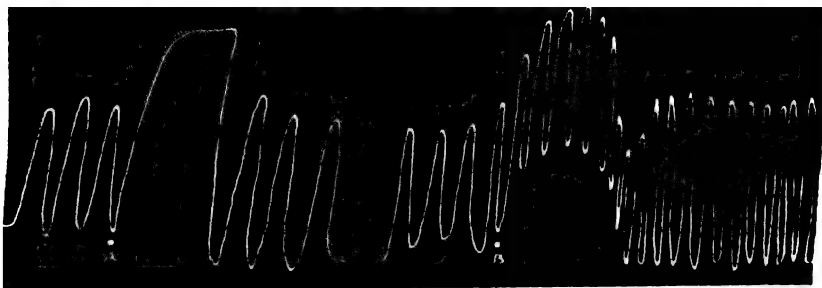


FIG. 87. *Isolated rat uterus* : Note the sustained (tetanic) contraction of the organ after ergometrine (A) and enhanced but rhythmic contractions after oxytocin (B).

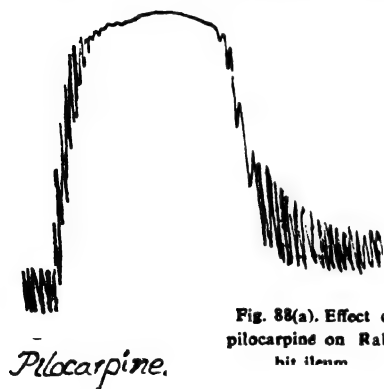


Fig. 88(a). Effect of pilocarpine on Rabbit ileum

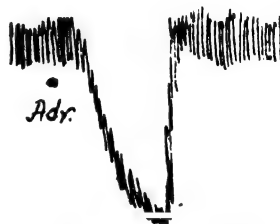


Fig. 88(b). Effect of adrenaline on Rabbit ileum

FIG. 88. *Isolated rabbit ileum* : Pilocarpine causes increase in tone whereas adrenaline causes reduction.

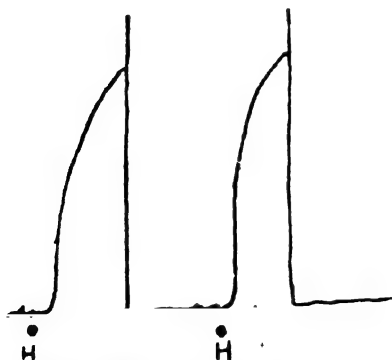


Fig. 89(a). Effect of Histamine on Guinea pig ileum

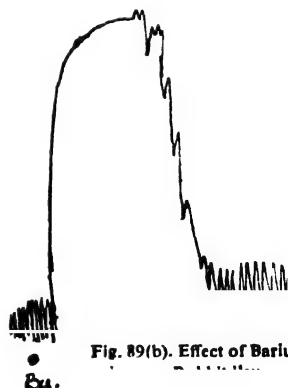


Fig. 89(b). Effect of Barium

FIG. 89. *Isolated guinea pig ileum* : Histamine and barium chloride both produce spasm. However, the action of the latter is slower.

Ergot and Pituitary Compared. The oxytocic effects of these two important uterine stimulants present a number of similarities with minor shades of differences: (a) *Ergometrine* is obtained from infected rye, while *pitocin* is the hormone of the posterior pituitary body. (b) Though the fluid extract of ergot is given orally, both ergometrine and posterior pituitary extracts are administered, mostly parenterally. (c) Both of them possess marked oxytocic action on uterine musculature (Plate XXXII, Fig. 87). While pituitrin action resembles more the normal labour pains in its onset, duration and nature, ergometrine is more spasmodic and of sustained nature in its contraction of the myometrium, endangering foetal life and uterine integrity, if used before the os is fully dilated. (d) For an ideal oxytocic, it is necessary that the drug action alternates with contraction and relaxation, enabling the fundus and the cervical muscles to work in a manner resembling normal contractions. This is achieved more by oxytocin than ergometrine and consequently, the former is used more during the delivery of the foetus and the latter after the foetus has already been expelled. (e) While the principal site of action of both the drugs is the myometrium, ergot action cannot be completely divorced from its sympathetic mechanism, while pitocin action is always a *direct* one. (f) Finally, the systemic toxic effect of ergot, however less with ergometrine, is greater than with the posterior pituitary extract. All these lead to greater and safer use of pitocin, in the earlier stages of labour.

Hydergine: It is the methane sulphonate of the hydrogenated base of ergotoxine, hydrogenation reducing toxicity but enhancing its adreno-sympatholytic effect on the smooth muscles. It acts as a central sedative, depress V.M. centre and produces B.P. fall. It is used in — (a) hypertension and (b) peripheral vascular disease. *Dose:* 0.3 — 1 mg. I.M., thrice a week.

Methergine: It is methyl ergonovine tartrate and soluble in water. It is similar to ergometrine but has less pressor effect. Its actions on the uterus are prompt — in $\frac{1}{4}$ minute after oral administration. *Tablets* of 0.2 mg and *ampoules* of 1 ml, are available for use.

Uses: The *major uses of ergot alkaloids* are only two: (a) *Oxytocic-ergometrine* and (b) *Sympatholytic-ergotamine* and derivatives.

- (i) Ergometrine finds its principal use, towards the end of the *third stage of labour* or better still, after the *delivery of the placenta* for controlling post-partum haemorrhage. *Ergometrine*, 0.25-

0.5 mg, I.M. is preferred, because of its more prolonged, spasmotic action and vasoconstrictive properties. *Methergine* is also sometimes used, in these conditions.

- (ii) *Ergotamine*, *DHE-45* and other derivatives, find their uses in *migraine* with characteristic hemicrania, vasomotor disturbances and increased cerebral pulsations. Dose: 0.25 ml. I.M. to a total of 1 mg/day or *tablets* of 1 mg/os to a total of 2-5 mg/day. The relief is spontaneous and appreciable, to the tune of 70-90 %, though of a palliative nature. They are also sometimes used in *thyrotoxicosis* and *hydergine* in *hypertension*, because of their sympatholytic action.

THERAPEUTIC DETAILS

Induction of Labour: Quite often the procedure starts with a dose of castor oil purgative, and quinine and is no more used these days. *Oxytocin* 0.5—2.0 ml. I.M. or more often, I.V. drip, in 5 % dextrose solution, containing 1-5 units/litre, given at the rate of 5-40 drops per minute. It should preferably not be used in the first stage and not till the os is fully dilated. It is also used in cases of uterine inertia with appropriate precautions about the absence of any disproportion between the presenting part and the pelvis.

Post Partum Haemorrhage: This is mainly due to secondary uterine inertia and has to be energetically handled by — (a) Evacuation of uterus and plugging, if considered necessary. (b) *Post pituitary extract* and more particularly, *Ergonovine* 0.2—0.5 mg. I.M., initially, followed by 0.2 mg. *sublingually*, t.d.s., for 7 days.

Diabetes Insipidus: It is a condition of disturbed water balance, characterised by polyuria and polydypsia, with passage of 10-12 litres of pale, low specific gravity urine in 24 hours. It is due to lesions of the pituitary gland or the adjacent parts of hypothalamus and may be *primary*, from the secretory deficiencies of ADH or *secondary* to pathological changes of inflammatory or neoplastic changes, involving the posterior lobe. The disease has a protracted course and if untreated, the patient dies of emaciation and intercurrent infections.

Its treatment consists of the administration of *pitressin tannat* in oil — 1 ml (5 mg) I.M., every 24 to 48 hrs. The action is palliative and relapses occur after the discontinuation of therapy.

ABORTIFACIENTS

Therapeutic measures employed for the termination of conception before the foetus is viable, are known as *abortifacients*. All the drugs used are unreliable and toxic.

Uterine Irritants: *Oil of savin* — obtained from *Juniperous savina* and used locally. It is a toxic drug producing abdominal pain, vomiting, diarrhoea and haematuria. *Drastic purgatives* — like croton oil and *Irritant diuretics* — producing considerable irritation of the pelvic organs including G.I. and genito urinary systems, are undependable and risky. Similarly, the *heavy metals* — like lead and others act by virtue of their cumulative effect causing foetal toxic manifestations.

Motor Stimulants: Oxytocid drugs — viz. *ergot*, *pituitrin* and *quinine* have very little action in the earlier stages of pregnancy, while sometimes being effective in the later stages of conception. *Endocrine preparations* of the oestrogen series — *progynon*, while acting better in the earlier stages, are not always effective.

Provocation of *therapeutic abortion*, if considered essential for the mother, should be performed under prescribed regulations by gynaecological measures of D. C. and not by any of the undependable drug therapy, referred above.

UTERINE SEDATIVES

These drugs reduce muscular activities of uterus and relieve dysmenorrhoea. *Corpus luteum hormone* possesses definite actions and will be studied later.

Two plants having some reputation as *uterine antispasmodic* are — (a) *Hydrastis* and (b) *Viburnum*, besides the use of — (a) Analgesics (b) Sedatives (c) Vitamin E and (d) Opium.

Hydrastis Canadensis: The 'golden seal', contains the alkaloids of berberine and hydrastine. The *Extract* — 0.3 — 1 gm. *Tincture* — 4 ml. and *Hydrastine HCl* — 15—60 mg., are seldom used, in therapeutics, these days.

They possess dubious actions of skin stimulant, bitter stomachic, haemostatic and febrifuge and have been used in G.I. catarrh, chronic alcoholism and as uterine sedative and haemostatic; but in all, with doubtful results.

Viburnum Prunifolium: *The liquid extract* — 4-8 ml, has been used as a sedative for neurotic and hysterical patients and as uterine antispasmodic, in habitual abortion, with doubtful efficacy. The role of *baudanum*, intrarectally, along with *vitamin 'E'* and *progesterone* as uterine sedative, in cases of threatened abortion, has been indicated elsewhere.

DRUGS ACTING ON THE MAMMARY GLANDS

The secretion of milk may be affected by a number of drugs, those increasing it, being known as *galactogogues* and those drying it up, as *antigalactogogues*.

Galactogogues: *Oestradiol* is responsible for development and *prolactin* for secretion of milk from the mammary gland. Prolactin, milk, sago, porridge, barley and good protein diet, are advocated for nursing mothers for increasing the yield of milk after parturition.

Antigalactogogues: *Oestradiol* and *Testosterone* block the anterior pituitary and decrease milk secretion. *Belladonna* and *atropine* are also reputed to reduce the secretion of milk and relieve engorgement of breasts. Strong purgatives, under nourishment, infection and excitement, may also decrease milk secretion and relieve mammary engorgements. *Belladonna plaster* is still used for the relief of breast engorgement and mammitis.

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SECTION

IX

PHARMACOLOGY OF THE DIGESTIVE SYSTEM

CHAPTER

37

GENERAL CONSIDERATIONS OF THE G.I. TRACT

PHYSIO-PATHOLOGICAL CONSIDERATIONS. NORMAL FUNCTIONS. COMMON DISORDERS AND DRUGS USED FOR THEM

[The digestive tract comprises a battery of secretory organs liver, pancreas etc. connected to a long muscular passage, known as gastrointestinal tract, possessing many vital functions. The latter is divided into an *upper*, *middle* and a *lower* portion, each subserving selective functions. Taken as a whole, the purpose of the digestive system is to accept or reject and also to digest food. The digested food is absorbed and the undigested residue voided out. The absorbed food is taken up by liver for storage and synthesis of vital substances and the remaining portion utilised by the peripheral tissues.

Digestion is carried out with a variety of enzymes, secreted by the different parts of the G.I. tract and the food is mixed with them and propelled by a series of ponderal, segmental and peristaltic movements. The functions of the digestive system can be studied by a series of tests which may help in the detection of diseases or discovering of drug action.

Digestive functions are affected by a large number of organic and functional disorders involving secretions or motility. Further, inflammatory and neoplastic conditions also occur. Drug treatment of most of these conditions, excepting probably the inflammations of an infective nature, are at best palliative. The need for finding out cures of digestive disorders, is of fundamental importance, because of their frequencies and impacts on the physical and mental status of patients in their day to day life.]

The digestive system is a long complicated arrangement for receiving, digesting, absorbing and rejecting food and also for voiding out unutilised faecal matters. The above processes are carried out by a series coordinated movements of the smooth muscles which mix the food with the digestive enzymes secreted by different parts of the gastrointestinal tract and then propel it forward.

The study of digestive function becomes difficult because of the enormous length of the G I. tract. None the less, the proximal and

distal parts, oesophagus and stomach, rectum and pelvic colon, can be visualised directly, whereas, the remaining parts can be examined by various chemical and radiological tests. The digestive system suffers from various disorders—many being of functional nature and several organic also. No wonder, therefore, that a large number of drugs are used for the treatment of digestive ailments with or without scientific basis always.

PHYSIO-PATHOLOGICAL CONSIDERATIONS: From a functional standpoint, the entire G. I. tract can be subdivided into 3 portions:

I. Upper Portion: (a) This includes the oral cavity, oesophagus, stomach and the proximal half of the duodenum. The function of this portion is to accept or reject food, to start its digestion and propel it forward.

(b) The saliva contains the enzyme ptyalin which acts on starch. The stomach secretes hydrochloric acid, pepsin, amyllopsin and lipase, which act only as proteolytic and amylolytic enzymes, carrying out partial digestion of proteins and fats. Parasympathomimetic drugs, histamine, insulin, alcohol, food and psychic impulses stimulate the formation of gastric juice. Besides, the stomach also produces an 'intrinsic factor' which helps in the absorption of vitamin B₁₂.

Methods of Study: (a) *Secretion*—the secretory ability of the stomach can be found out by inserting a Ryle's tube into the stomach and aspirating the gastric contents. The levels of free, combined and total acidity are then estimated. This gives an idea of the resting secretion of the stomach. To find out the ability of the stomach to secrete under conditions of stimulation, a test meal, alcohol, subcutaneous insulin (7-10 units) or histamine (0.5 mg) is administered and analysis of gastric acid is carried out repeatedly, at fixed intervals. This procedure is known as *fractionalgastric analysis*. The ability of the stomach to secrete hydrochloric acid, increases in *peptic ulcer* and is reduced in *pernicious anaemia* and *carcinoma* of the stomach. In the last two conditions, the acid secretion does not occur even after the injection of histamine. This is known as *achylia gastrica*.

(b) *Motility:* This can be studied by asking the patient swallow a radio opaque barium sulphate. The outline of the stomach can then be made out with the help of X-ray screening. Any irregularity of the mucous lining or deformity of the duodenal cap, due to ulcer, can be made out. Similarly, the presence of carcinoma or hypermotility can also be determined.

(c) *Endoscopic examination*: The interior of the oesophagus or stomach can be visualised by inserting an oesophagoscope or gastroscope.

(d) *Animal experimentation*: (i) Certain portions of the stomach can be exteriorised for direct view and the secretions of this portion can be readily collected. This procedure is called *fistula* formation.

(ii) The pressure changes within the stomach can be studied by inserting a rubber balloon connected to a pressure measuring device.

(iii) Alteration of blood supply of the stomach, which happens during emotional changes and after meals, reflect as changes in stomach temperature. This can be measured by means of a *thermocouple*, inserted into the stomach.

Common Disorders: (a) *Malignancy*: can occur in the oral cavity, oesophagus and stomach.

(b) Obstruction to the passage of food can occur in achalasia cardia and pyloric stenosis.

(c) Secretory ability of the stomach may be reduced in pernicious anaemia, carcinoma of the stomach, and more commonly, as a functional derangement in a large number of cases suffering from indigestion, flatulence etc. termed as *dyspepsia*.

(d) Peptic ulcer is due to a complex etiology of hyperacidity and increased enzyme secretions, associated probably with reduced ability of the mucous membrane lining of stomach and duodenum to protect itself.

(e) Medical treatments of the above conditions are at best symptomatic and palliative. The obstructive conditions, may sometimes be relieved by antispasmodics, hypochlorhydria by dilute hydrochloric acid, dyspepsia by stomachics and digestants and peptic ulcer by antacids, antispasmodics and regulated diet.

II. Middle Portion: (a) This extends from the mid-duodenum to the ileocaecal sphincter. Digestion of food in this part is aided by the presence of bile and alkaline pancreatic secretions which are poured into the mid-duodenum, and also succus entericus produced in the small intestine. During its passage through the middle portion, the partially digested food is acted upon by a series of enzymes trypsin and erypsin (proteolytic), invertase (saccharolytic) and lipase (fat splitting) and when their digestion is complete, the end-products viz. amino acids, glucose, fructose and fatty acids, along with water and other substances including drugs, capable of absorption, are extensively absorbed, to the extent of 90%, from the small intestine. The

secretions of this portion, again, are under the influence of the parasympathetic system.

(b) Food, in the middle portion, is mixed and propelled by means of a series of movements which are of three types: (i) pendular, (ii) segmental and (iii) peristaltic.

(i) *Pendular* movements are due to the contraction of the longitudinal muscle fibres occurring at a rate of 10/min. In the intact state, this movement may be reflected as the swaying of the loops and is not very important from the functional standpoint. This is the movement which is usually recorded in experiments on isolated intestine.

(ii) *Segmental* movements are nonpropulsive local contractions of circular muscles, occurring rhythmically. This movement helps in the mixing of food with the secretions.

(iii) *Peristaltic* movements are propulsive and occur at a rate of 5-10/min. This is a coordinated and complex contraction of the circular muscle fibres and is caused by the presence of a network of nerve fibres and parasympathetic ganglia in the wall of the small intestine, known as the *Auerbach's* and *Meissner's plexuses*. The motility of the small intestine is increased by the parasympathetic stimulants and irritant purgatives and the intestine is thrown into a spasm as in lead poisoning or by opium.

(c) Absorption, which is an important function of this part of the intestine, is helped by the enormous increase in the absorptive surface due to the presence of small villous projections. The absorption of fats is facilitated by the secretion of bile which possesses emulsifying properties.

Methods of study: (a) The secretions can be collected from the duodenum and small intestine by inserting suitable tubes and their contents may then be estimated.

(b) *Blood studies:* help in certain inflammatory conditions like pancreatitis in which the digestive enzymes may leak into the blood.

(c) *Pressure changes* can be studied by means of balloons.

(d) *Experimental studies:* In this, the contractions of the intact or the isolated loop of the intestine may be recorded for studying the effects of drugs. Fistula can also be produced for studying the secretory changes in the intestine.

Common Disorders: (a) Malignancy is conspicuous by its rarity, in this portion.

(b) The common conditions are inflammatory in nature e.g. *typhoid*, *tuberculosis* etc.

(c) Ingestion of irritating food substances may cause *colicky pain* and *diarrhoea*.

(d) Obstruction to the flow of the bile juice may be due to stones in the bile duct.

(e) Pancreatic function may be affected in malignancy and pancreatitis.

(f) Treatment of these conditions is specific in most of the cases of infective disorders. Symptomatic treatment may be given for intestinal colic, in the form of antispasmodics.

III. Lower Portion: This comprises caecum, ascending, transverse and descending colon, rectum and also the anal canal. This part is chiefly concerned with the absorption of water, giving faeces its final characteristic. By means of mass peristalsis, it is then voided out at intervals of usually once or twice a day, depending upon the habit of the person.

Methods of study: (a) Motility of the lower portion of the gut can be studied either by the *balloon technique* or after giving a meal or enema of barium sulphate, followed by *radiological* observations. Anatomical defects, as well as morphological changes brought about by diseases like malignancy and tuberculosis, can thus be visualised.

(b) The anal canal, rectum and sigmoid colon can also be directly *visualised* by means of *proctoscopic* and *sigmoidoscopic* examinations. With the help of these, the diseased parts can be identified and specimens collected for histological or bacteriological studies.

Common Disorders: (a) One of the most important functional disorders of this part is constipation, in which, the person has difficulty in defaecating. The underlying defect may be an obstruction in the passage, associated with colicky pain or lack of tone in rectum known as dyschaezia.

(b) An organic defect in the nerve plexus of the rectum, resulting in atonia and severe constipation, occurs in children and is known as *Hirschsprung's disease*.

(c) Infective conditions are exemplified by bacillary and amoebic dysentery.

(d) Chronic colitis and ulcerative colitis may also occur. Finally, malignancy is fairly common in this part of the G. I. tract.

(e) Drug treatment for constipation comprises the judicious use of laxatives. Proper high residue diet should be prescribed. Amoebic and bacillary dysentery may be treated with the appropriate specific drugs and ulcerative colitis with cortisone. Malignancy, *Hirschsprung's disease* as well as ulcerative colitis, require surgical intervention.

Liver: Though it is a distinct organ anatomically, still a large number of hepatic functions are related with the digestion. Apart from these,

liver plays the part of a versatile chemical laboratory which destroys toxic substances and drugs, synthesises vital substances like plasma proteins for the body and stores food material and certain vitamins.

The liver has a complicated network of blood vessels and canaliculi, interlacing with the syncytial arrangement of cells. Arterial blood comes from the hepatic artery and represents about 15-20% of the total hepatic blood flow. The major source of blood is the portal vein. This blood, laden with absorbed food, comes from the gastrointestinal tract. The hepatic cells secrete bile into the canaliculi and this is ultimately poured into the duodenum after being concentrated in the gall bladder.

Bile, containing bile salts, has emulsifying properties and consequently, it aids in the absorption of fat, as well as, fat soluble substances. Liver detoxifies poisonous substances, either by oxidising or reducing them or by conjugating them with sulphate or glucuronic acid, to form inert substances. This latter process of conjugation is also known as *protective synthesis*. Due to all these effects of the liver on the metabolism, it plays a buffering role on the level of the blood sugar as well.

Factors affecting liver function: (a) Due to the peculiar arrangement of blood vessels in the liver, certain cells get very little oxygen and are on the verge of *hypoxia*. Any factor lowering the blood oxygen content or poisons like carbontetrachloride, aggravate this further, causing liver damage.

(b) The liver may become *inflamed* also due to virus, bacteria, protozoa (amoeba) and poisons. Certain types of inflammations lead to a distortion of the architecture of the liver resulting in the obstruction of the flow of blood through the portal system. Such a condition is known as *cirrhosis* of the liver. The portal obstruction leads to portal hypertension, which in turn, results in the transudation of fluids from the capillaries into the peritoneal cavity, causing *ascites*.

(c) Certain normal constituents of *diet*, like essential aminoacids, glucose and methyl donors like *choline* and *methionine*, serve the purpose of protecting the liver from damages. Any deficiency of these or excessive consumption of fats or alcohol, can result in hepatic derangement.

Liver function tests: These are many and are designed to test individual functions like synthesis and excretion of the liver. They are:

- (a) galactose tolerance test. (b) hippuric acid synthesis test.
- (c) bromosulphthalein test. (d) prothrombin response after Vit. K.
- (e) serum protein estimation. (f) flocculation tests.

Hepatocellular Failure: (a) It may occur in any condition which grossly damages the liver, as in *infective hepatitis* and advanced *cirrhosis*. If it is slowly developing, then, there may be indigestion, progressive drowsiness, fever, reduced blood pressure, increasing jaundice, bad smell of breath, followed by coma. In rapidly developing hepatic failure, there may be initial excitement followed by coma.

(b) In advanced cases of hepatocellular failure, accumulation of ammonia in the blood and brain results in a peculiar *neuropsychiatric syndrome*, characterised by drowsiness, flapping tremors, absence of deep tendon reflexes etc. This syndrome is increased by giving proteins and reduced by inhibiting ammonia formation by destroying the intestinal flora with neomycin.

(c) Drugs used for treating the depressed liver functions are known as *liver protectives*. Their exact role is still not clearly known and their therapeutic status is far from established.

PHARMACOLOGICAL CONSIDERATIONS: The various drugs used in digestive disorders, depending upon their action, can be grouped as follows:

Drugs modifying
secretory functions

Sialogogues and antisialogogues
Stomachics and antacids
Cholagogues and choleretics

Drugs modifying
digestion

Digestants

Drugs modifying
gastro-intestinal
motility

Carminatives
Purgatives
Astringents

Drugs affeting
liver functions

Liver poisons
Liver protectives

CHAPTER

38

PHARMACOLOGIC RESPONSES IN MISCELLANEOUS G. I. DISORDERS

SIALOGOGUES, STOMACHICS, DIGESTANTS CARMINATIVES AND ADSORBENTS NUTRIENTS, LIVER POISONS AND PROTECTIVES. TREATMENT OF DYSPEP- SIA AND HEPATIC FAILURE

[The complex function of digestion and assimilation of different types of food involves coordinated working of different parts of the G. I. tract, as well as of the accessory organs. Besides the mechanical role of the mouth, stomach and the intestine, a large number of secretions—saliva, gastric, pancreatic, intestinal juices and bile, also have to play their parts in this process of chemical and enzymatic reactions. It is thus natural that some of these are disturbed in diseased conditions breaking the link in these chain reactions, requiring drug therapy.

The *sialogogues* increase the salivary secretion. These are bitters, cholinergic drugs and also chemical agents like Hg, KI. The *antisialogogues* are the astringents—borax, alum, kramaria—which are sometimes used as gargles in sialorrhoea. Atropine in high doses, also produces dry mouth.

The *stomachics* are the simple, aromatic, astringent and alkaloidal bitters which increase the gastric secretion often from increased salivary secretion. They are calumba, gentian, orange and lemon peels, nux vomica and cinchona, which are used for increasing appetite and digestion in atonic dyspepsia and hypochlorhydria after acute illnesses or otherwise.

The *digestants* are mostly the enzymes—pepsin, papain, pancreatin and diastase and also bile, dehydrochloric acid and polysorbate 80, which, along with HCl dil are used for the treatment of dyspepsias.

The *carminatives* comprise essential oils of peppermint, cinnamon, cardamom, camphor, asafoetida, ginger and also sodabicarb, spt. ammon. aromat and aqua chloroformi. They expel gas from the stomach and intestine and correct wind colic.

The *adsorbents* adsorb gas and relieve fermentation and colic pain. Charcoal, kaolin, magnesium trisilicate are mostly used.

The *nutrients* comprise malt extract, marmite, peptonised milk and protein hydrolysates, while the *colouring* and *sweetening agents* are cochineal and saccharine respectively.

The liver with all its secretory, excretory, synthetic and detoxicating functions, is destined to be affected by drugs and poisons. The halogens, metals, cinchophen and biological toxins of malaria and kalazar act as *liver poisons* producing inflammatory and necrotic changes. For this, *liver protectives* like choline, methionine, inositol, folic acid, vitamin B₁₂ and lipocic, a pancreatic extract, are sometimes used with mixed results. In *acute hepatic failure*, cortisone, I.V. glutamic acid and antibiotics are of value. In *hepatic coma*, also, the same treatment is advocated. The outcome in both these conditions is, however, gloomy.]

SIALOGOGUES

These drugs augment the salivary secretion by mechanisms already outlined under 'general considerations'. They themselves are not of much therapeutic value but as the salivary secretion initiates gastric secretion, involving common physiological mechanisms, they will be dealt with very briefly.

Mode of Action: The sialogogue effect is producible by any of the following mechanisms:

1. *Reflexly* from sight, thought, smell, taste and also sometimes by strong disgust, tending to induce vomiting and sweat. *Vegetable bitters*, simple and aromatic, come under this category. It is also producible from the mechanical act of chewing, probably through the gustatory reflexes.

2. *A. N. S.*: Ganglionic stimulation by nicotine provokes secretion of mixed type of saliva. Cholinergic responses from pilocarpine, eserine and acetylcholine produce thin watery secretion. Adrenergic responses from the sympathomimetic drugs produce thick, viscid saliva. Thick saliva is produced by food and is intended to help digestion, while watery saliva is more suited for washing up and deglutition of food.

3. *Chemical agents*: Mercury, iodides and most of the heavy metals, as cumulative poisons during the process of their buccal excretion, enhance salivation.

Uses: Very rare: flavoured sweets, lemon drops, lemon peel, retained in the mouth, relieve parched throat in singers and orators or in cases of salivary calculi.

ANTISIALOGOGUES

These are mostly the 'astringent gargles' of borax, alum, tannic acid or kramaria, which decrease salivation and are used in cases of sialorrhoea from buccal or gingival ulceration. Atropine in large doses, also paralyses the secreto-motor fibres, but due to side-effects, is seldom used. Morphine, hyoscine, potassium chlorate and other astringent metals, also possess antisialogogue action.

STOMACHICS

Drugs which increase the secretion of gastric juice, are called stomachics, irrespective of whether the increase is secondary to the increase of salivary secretion, which is often the case, or otherwise.

It is true that a very large number of widely grouped agents are capable of increasing gastric secretion and more particularly, the secretion of hydrochloric acid, viz the parasympathomimetic agents, histamine, alcohol etc. but the term stomachics particularly refers to the *vegetable bitters*, which alone are used therapeutically, for this effect.

CLASSIFICATION

Simple bitters	Calumba, quassia, gentian, chirata
Astringent bitters	Serpentary, atristolachia, kalmegh
Aromatic bitters	Orange and lemon peel, absinth, betel, cascara.
Alkaloidal bitters	Quinine, strychnine

<i>Preparations:</i> Tinct. Gentian Co.	—	2-4 ml
Infusio Chiratta Co.	—	15-30 ml
Infusio Calumba	—	2-4 ml
Tinct. Aurantii	—	1-2 ml
Syrup Aurantii	—	2-4 ml

The parts of these plants used for the preparation of medicines are: gentian root, quassia wood, chiratta dried plant, calumba sliced root, orange and lemon peels or cortex and aristolochia rhizome.

Action and Uses: These substances stimulate the taste buds in the tongue because of their bitterness and reflexly increase the secretion of saliva and gastric juice, but not enzymes. As a consequence, appetite is sharpened and digestion is improved. Hence they act as sialogogues, stomachics and appetisers. The bitters have no action on the stomach and when introduced directly through a stomach tube, they produce no increase of gastric secretion. Their efficacy is increased when they are combined with the aromatics and alcoholic preparations. Large doses, as well as, continued uses, derange the digestion by producing gastric irritation.

Bitters are largely employed to promote appetite and digestion in atonic dyspepsia, associated with hypochlorhydria, specially during the period of convalescence from an acute illness or after prolonged mental stress. They are administered either as infusion or tincture, often combined with dilute hydrochloric acid or sodium bicarbonate and taken within half an hour before the principal meals. Being free from tannin, quassia, calumba and chirata can be given with iron salts. In general, bitters are contra indicated in all diseases of the

stomach accompanied by pain, vomiting, inflammation or ulceration, namely, gastritis and gastric ulcer.

Freshly prepared infusions of quassia or calumba has been used per rectum as an anthelmintic for thread-worms but their uses have been discontinued. The tinctures and syrups of aromatic bitters are mainly used as flavouring agents and carminatives.

DIGESTANTS

They belong to two groups—(a) *Proteolytic*—pepsin, pancreatin and papain and (b) *Amylotytic*—Taka diastase.

Pepsin: It is obtained from the submucous layer of the cattle stomach. It is a buff coloured, amorphous powder, with a meaty taste and moderate solubility. *Dose:* 0.3—1.0 gm., a good sample digesting about 3000 parts of coagulated egg albumin.

Preparations: Pulv. Pepsin Co. — 0.6-2.0 gm
Glycer. Pepsini. — 2-4 ml

Papain: is obtained from the latex of unripe carica papaya. The *dose* of papain is 0.12—0.16 gm. and of the *elixir*—2-4 ml.

Both pepsin and papain can be used as substitutes for deficient gastric ferments. Pepsin should be used along with acid hydrochloric dil. 1-2 ml after meals. Papain acts better in a neutral medium and is a good substitute for pepsin when strong religious objections prevail. These enzymes retain their potency with difficulty and their real efficacy is also controversial. It is much better to use HCl instead, which converts pepsinogen to pepsin in the stomach.

Pancreatin: It is prepared from the cattle pancreas in alkaline medium and is an amorphous powder, to be kept in cool places. *Dose:* 0.18-0.6 gm. Liq. pancreatini: 2-8 ml. and Pulv. pancr. Co.—1.5 gm/500 ml for the preparation of peptonised milk.

Uses: (a) Bacteriological work, (b) Preparation of peptonised milk and (c) Treatment of dyspepsia.

Takadiastase: It is an important digestant, obtained by the cultivation of an aspergillus, *Eurotinum oryzae* on brans. A yellowish-white powder with a *dose* of 60-300 mg. It is an amylolytic enzyme which can change 100 times its own weight of starch to maltose in a few minutes. It is useful in *starchy dyspepsia* in rice eating population.

Bile and Bile Salts: *Extractum Fellis Bovini* or ox bile, is prepared by evaporating fresh bile to one fourth, its volume after removing mucous with 90% of alcohol. It contains bile salts and pigments. Dark yellowish-green, of bitter and disagreeable taste. *Dose:* 0.3-1.00 gm.

It is absorbed from the intestine and excreted in gut and urine. It helps in the digestion of fat by the activation of the pancreatic enzyme, as well as, by the absorption of fat soluble vitamins and calcium. It is choloretic, cholagogue, a mild intestinal antiseptic, laxative and is best used in the form of keratin capsules or salol varnished pills after meals.

Dehydrocholic Acid: It is obtained by the oxidation of cholic acid. *Dose:* 0.25-0.5 gm. tds., after meals, in cholecystitis and cholangitis with biliary stasis. The sodium salt is used for determining the arm to tongue circulation time, after I. V. injection.

Polysorbabte 80: An oleic acid ester of sorbitol, it is a good emulsifying agent and is used in steatorrhoea, accompanying sprue and coeliac disease, in doses of 2 gm capsules, after meals.

Treatment of Dyspepsia: It is an annoying condition affecting patients of all ages and is associated with loss of appetite due to deficient acidic and enzymic secretion in the digestive system. The condition usually follows exhausting and debilitating diseases and may need the use of the following drugs judiciously administered:

(a) *Bitter tonics*, given before meals for causing reflex increase of salivary and gastric secretions. (b) *Demulcents*, olive oil, kaolin and also sod. bicarbonate for preventing excessive mucous secretion. (c) *Dilute hydrochloric acid* (1-2 ml.) for correcting the hypochlorhydria. (d) *Pepsin, pancreatin and taka diastase*, as digestive ferments and finally, (e) Simple, easily digestible, nourishing food, the bowels being kept open with mild laxatives.

CARMINATIVES

These substances are used for the treatment of flatulence and colic by expelling the gases from the stomach and the intestine. They relieve the feeling of discomfort and distension after meals, (i) by opening out the cardiac or the pyloric sphincters, correcting irregular peristalsis (ii) by decreasing tone and spasms of the intestine and (iii) by expelling the wind from the G. I. tract. Most of the carminatives contain volatile oils and their action may be due to their irritant properties on the stomach.

The carminatives comprise two different groups of drugs:

I. *Volatile oils* or volatile oil containing substances or their preparations: oils of peppermint, anethi, cinnamon, clove, fennel, coriander, caraway, nutmeg; camphor, menthol, thymol and also asafoetida and ginger.

II. *Chemical drugs*: Sodium bicarbonate, aerated water, spirit ammon, aromaticus, aqua chloroformi.

VOLATILE OILS

These are the *essential* or *aromatic* oils which are obtained by steam distillation of aromatic plants. They possess the following general properties:

- (a) All of them stimulate the salivary and the gastric secretions and also possess carminative actions.
- (b) They act as irritant, rubefacient and also reflex stimulant of the central nervous system.
- (c) They have some local anaesthetic and antiseptic action which may be due to their volatile nature and solubility in bacterial lipids.
- (d) They possess a mild degree of diuretic, as well as urinary and pulmonary antiseptic action.

Chemically they are divided into two groups

(a) *Elaeoptenes*, available in liquid forms.

(b) *Stearoptenes*, available in solid forms, as in the case of, : (i) Resins—colophony, (ii) Oleoresins—copaiba, (iii) Gumresins—asafoetida, myrrh, storax, (iv) Balasams—benzoin and peru, (v) Tar oils, (vi) Camphor, thymol and menthol.

The activities of volatile oils are due to the presence of phenols, aldehydes and ketones, which belong to terpene and sesquiterpene organic groups.

Though they are at present only a legacy of age-old remedies, *therapeutically*, they represent a large number of drugs, arranged under the following groups:

Carminative and intestinal antispasmodics	Oils of clove, nutmeg, cinnamon, lemon, capsicum, ginger, cardamom anisi, coriander, caraway, fennel lavender, peppermint and betel
Nauseants and nerve sedatives	Asafoetida and valeriana
Genito-urinary antiseptics and diuretic	Copaiba, sandalwood, buchu, juniper and cubeb
Pulmonary stimulants and antiseptics	Balsam of peru, tolu and storax
Skin irritants	Terpentine, oil of casde, mustard, cajuput, eucalyptus, rosemary and capsicum
Anthelmintics	Oil of chenopodium, terpentine and thymol

Mentha Piperita: Oil, distilled out of mentha piperita flower tops. *Dose:* 0.06-0.2 ml *Preparations:* Aqua—concentrated—0.3-1 ml. and destillata—15-30 ml.

Action and Uses: The presence of menthol imparts a sensation of coldness, numbness and then warmth and allays neuralgia pain and toothache. *Internally,* it is antispasmodic and carminative and is used in flatulent colic and also as a vehicle.

Ginger: The dried rhizome contains aromatic oil and gingerol. *Dose:* 0.3-1.0 gm.

Preparations: Tinct. zingiberis fortis 0.3-0.6 ml.
Tinct. zingiberis mitis 2.0-4.0 ml.
Syrup zingiberis 2.0-8.0 ml.

It enters into *Puly. jalap Co.*, *Pulv. rhei Co.* and in carminative mixtures for infants.

Action and Uses: an aromatic stimulant and sialogogue of the type of capsicum and cardamom and is used as a stomachic, carminative and flavouring agent.

Cardamom: Tinct. card Co.—2 4 ml. is a carminative, colouring and flavouring agent.

Anethum: dried ripe *Anethum fructus* or dill fruit.

Preparations: Ol. anethi 0.06- 0.2 ml.
Aq. anethi dest. 15.00-30.0 ml.
Aq. anethi conc. 0.3 - 1.0 ml.

Action and Uses: An aromatic carminative which relieves flatulence and colic pain in children. It is incorporated in many gripe mixtures or cures for infants.

Myristica: the dried kernel of nutmeg or *jaiphal*. *Dose:* Powder 0.3-0.6 gm. and oleum myristicae—0.06-0.2 ml. It is a perfuming agent, a carminative and also used for the relief of toothache.

Cinnamomum: The dried bark of *dalchini*. *Dose:* Powder—0.2-1.3 gm. 0.1. cinnamomi—0.06-0.2 ml. and Aqua—15-30 ml. It enters into Pulv. creta aromat. and Tinct. card Co. It is used in tympanites of typhoid fever.

Caryophyllum: The dried flowering buds of *Eugenia aromatica*, containing volatile oil, caryophyllin, gallo-tannic acid and resin.

Oleo caryophylli	0.6-0.2 ml.
Infus. caryophylli conc.	2-4 ml.
Infus. caryophylli recens	15-30 ml.

It also enters into *Pulv. Creta aromatica*.

Externally, it is a stimulant, rubifacient, counterirritant, anaesthetic and antiseptic and *Internally*, digestive, carminative, and intestinal antispasmodic. It is used as an anodyne in superficial neuralgias and toothache and also in intestinal colic and flatulence.

Asafoetida: An oleo-gum resin, obtained from *Ferula foetida*. *Dose:* 0.3-1.0 gm.

Preparations: Pil Aloes et Asafoetida: 0.25-0.5 ml.

Tinct. Asafoetida 2.0-4.0 ml.

It is a carminative, antispasmodic and reflex C.N.S. stimulant.

Valeriana: The dried rhizome and root of *Valeriana officinalis* contains 1% of volatile oil. *Dose:* 0.3-1 gm. Tr. valerianae ammoniata—2-4 ml. It is a sedative and has also been used in hysteria, along with bromides and camphor monobromatum.

Storax: A brown, viscous balsam, soluble in alcohol. It enters into tinct. benzoin Co.

Balsam of Peru: A viscid, dark brown, insoluble substance, containing cinnamic and benzoic acids. It is an antiseptic and stimulant expectorant and is used also for sore nipples and cracked lips.

Oil of Cade: or juniper tar oil; black, viscid and of aromatic taste. It is sometimes used in the form of an ointment for chronic eczema, psoriasis and other skin diseases with itching. It is also a skin irritant.

Oleum Cajuputi: Yellow liquid of camphoraceous odour. *Dose:* 0.06-0.2 ml. Spt. cajuputi—0.3-2 ml.

It is a carminative and antispasmodic and is used in flatulent colic with intestinal spasms.

Menthol: Natural and synthetic, Prismatic crystals and soluble in alcohol.

Preparations: Spt. mentholis Co.—10 drops by inhalation. Also insufflatio and nebula mentholis, used for bronchitis and laryngitis.

Action and Uses: It is cooling and anodyne for skin and is used in the form of menthol ointment or liniment, in cases of prurigo, sciatica and lumbago. Menthol with thymol, phenol and chloral hydrate forms an oily liquid, used in toothache from carious teeth. It is also a powerful antiparasitic drug for ringworm of scalp.

IMPORTANT PREPARATIONS AT A GLANCE

<i>Preparations</i>	<i>Dose</i>	<i>Use</i>
Aqua anethi distillata	15-30 ml	— Flatulence of children.
Aqua menthae piperata	15-30 ml	— Flatulent griping colic.
Aqua cinnamoni conc.	0.3- ml	— Tympanites of typhoid.
Tinct. cardamom co.	2- 4 ml	— Carminative, flavouring and colouring agent.
Tinct. zingiberis	2- 4 ml	— Antispasmodic.
Tinct. asafoetidae	2- 4 ml	— Antispasmodic and carminative.
Aqua chloroformi	15-30 ml	— Carminative, flavouring agent and vehicle.

CHEMICAL DRUGS

These are principally three: Sodium bicarbonate, Spt. ammon. aromaticus and Aqua chloroformi, studied elsewhere. Soda bicarb, given orally, releases CO₂ and acts as a carminative and also gastric and systemic antacid. Spt. ammon. aromaticus contains NH₄ which is the carminative principle, while aqua chloroformi action is based on the principle of volatile oils.

Carminatives Summarised: (a) with the exception of the three chemical drugs, most of the carminatives belong to the group of volatile oils

or substances. (b) The dose of the oils is usually—0.06 to 0.3 ml. and their aqueous or tincture preparations are mostly used, the dose of the former being 15-30 ml. and that of the latter—2-4 ml. They mostly act by correcting irregular peristalsis and by their antispasmodic action. (c) Aqua anethi dest. and Aqua menthae piperata are preferred for the relief of flatulence and as gripe cure in children, Aqua cinnamonii con. (0.3-1 ml.) in tympanites of typhoid fever, Tincture Card. Co. is also a flavouring and colouring agent. Tincts zingiberis and asafoetida as antispasmodics and Aqua chloroformi also is a flavouring agent and a vehicle for mixtures. (d) Relief of wind colic, aerophagy and abdominal distress from the obstruction in the passage of the wind, either of gastric or intestinal origin, are their principal indications in therapeutics, without precluding, however, the use of other antispasmodics, gastric sedatives and adsorbents, which also bring about relief in similar cases.

ADSORBENTS

These are preparations which possess the property of adsorbing gastric and intestinal gases due to their physical character of porosity and chemical nature. They are sometimes used in cases of fermentation, wind colic and aerophagy, in which last condition, a patient of nervous and hysterical nature, swallows a good deal of air and suffers from air colic.

Insoluble bland powders—bismuth salts, chalk, kaolin in large doses, as suspension and also gelatinous exudates like acacia, plantago ovata, may be used, for their astringent and demulcent effects.

The removal of gases, toxins and other substances of poisonous nature, from the stomach and the intestine is a physical phenomenon shown by the colloidal particles, whereby, substances are made to adhere to the adsorbent. The large surfaces of colloids help in this process. The gas masks, used at times of warfare, are also prepared on this basis.

The important adsorbents deserving considerations are only three—(a) Carboligni or wood charcoal, (b) Kaolinum or aluminium silicate and (c) Magnesium trisilicate or magsorbent, which are detergents.

Charcoal (Carboligni): 4-8 gm. is made by burning wood in the presence of minimum oxygen. Activation by heating in steam or at high temperature for a few hours, increases its adsorptive capacity.

Kaolin or china clay (aluminium silicate): 15-60 gm. acts as an astringent and demulcent.

Magnesium trisilicate: 0.3-2 gm. is a powerful adsorbent, antacid and demulcent. Talc. or hydrated magnesium silicate is widely used as dusting powder also, because of its adsorbing properties.

NUTRIENTS

A number of substances which are easily assimilable and offer adequate energy and nourishment to the debilitated, convalescing patients or to those who cannot take solid food in its usual form, are used as nutrients, by enteral or parenteral routes. Sucrose, glucose, lactose, lecithin, malt and marmite, protein hydrolysates, peptons and peptonised milk, are some of these substances.

Sucrose: or ordinary sugar is obtained from beet roots and sugar cane. It is readily soluble in water giving a syrup of 66% strength, which is a good preservative for pharmaceutical preparations. Common sugar is a calory and energy yielding, fattening agent which also possesses mild diuretic effect. It however produces fermentation in the intestine and should not therefore be used for a long time.

Lactose: or sugar of milk. Sol. 1 in 7. It is sometimes used for babies and also for dilution of potent drugs. It is much less sweet than cane sugar and can be used by the diabetics and also in wasting diseases.

Dextrose or Glucose or grape sugar, is prepared by the hydrolysis of starch (sol. 1 in 1) Liq. glucose contains dextrose, dextrine, maltose and water. Strength—33%.

It is readily assimilable and is a good source of energy. It also helps in the combustion of fat and protein and combats acidosis. In 5% sol., it is isotonic. The hypertonic solution is used for reducing intracranial pressure. It protects liver and heart against toxins and is used with strophanthin, in cardiac conditions. It is also used in acute illnesses and diabetic coma, along with insulin.

Gelatin: translucent sheets, prepared from skin, tendon and ligaments. Gelatinum zinci contains 2% of gelatin and Unna's paste, contains ZnO and gelatin, 15% each. Gelatin is used as a basis for preparation of pessaries, suppositories, capsules, and also pill coating and preparation of jellies. It spares proteins but contains no tryptophan. It is a haemostatic.

Lecithin: Yellow waxlike substance, ovolcithin is prepared from egg and brain. It is broken down by pancreatin to glycerophosphates

and choline and has some nutritive value for the nervous system. It improves R.B.C., haemoglobin, body weight and general nutrition. Its real efficacy is doubtful, though used in many proprietary tonics.

Malt Extract and Marmite: They are prepared from *Hordium distichon* (barley) and brewer's yeast, respectively. *Dose:* 4-16 gm. Yellowish-brown, sticky consistency, agreeable and tasty. Extr. malti with ol. morrhuae. Extr. malti with ol. vitaminato—4-16 ml.

Malt supplies predigested carbohydrate and marmite is a rich source for vitamin B complex. They are also used as basis for many popular infant foods and for debilitated persons, suffering from wasting diseases and also during convalescence.

Peptonized Milk: It is prepared with milk—1 pint, liq. pancreatin 5 ml. sodabicarb 1.3 gm. It is then digested near the hearth for 15' or at room temperature, for 3 hours. The temperature is then raised to the boiling point for arresting further digestion. Peptonised milk is used as a predigested food for cachectic and convalescing patients.

Protein Hydrolysates: A number of amino acids are essential for the synthesis of tissue proteins. Protein hydrolysate, which contains—(a) tryptophan, (b) cystin, (c) thiamin, (d) riboflavin and (e) nicotinic acid, is very useful for starved and wasted patients with G. I. troubles, persistent vomiting, peritonitis, peptic ulcer, cirrhosis and ulcerative colitis, who cannot assimilate ordinary proteins.

It is prepared from casein by papain hydrolysis at pH 5-7, at 50°C. It may be prepared from meat also after 24 hours of digestion. The optimum digestion is determined by *formol titre* test by heat coagulation and the preparation is standardised. Special preparations are (a) Amigen, (b) Parenamine. *Usual dose:*—200-300 ml. to a maximum of 1200-1400 ml./day. I. V. It is of very high nutritive value but is contraindicated in nephritis cases.

COLOURING AND SWEETENING AGENTS

Cochineal: the dried female insect, *Coccus cacti*, gives a dark red powder, containing carmic acid and carmin, which act as colouring matter, turning to purple with alkalis. *Tinct. Cocci*—0.3-1 ml. is usually used. It enters into—(a) *Tinct. card. Co.* (b) *Tinct. Cinchona Co.* and gives beautiful colour to the preparations.

Saccharine: A white crystalline powder, intensely bitter but gives sweet taste on dilution. *Dose:* 30-120 mg. It is a sweetening agent,

acting as a substitute for sugar in cases of (i) diabetes and (ii) obesity. It also masks the bad taste of unpleasant drugs. It has however no caloric value like sugars.

LIVER DRUGS

There is hardly any other organ which possesses more complex biochemical activities in the body than the liver. Since the days of Claude Bernard, more and more functions of this organ are being discovered and yet much more has yet to be unveiled before the organ can be fully understood.

The metabolic functions of liver, comprising synthesis of ammonia from amino acids, glycogen storage, formation of phospholipins and choline, storage of AAP, formation of heparin and prothrombin, the pigmentary and detoxicating functions, these are only a few of the numerous activities of this vital organ. Yet it is really astonishing how these batteries of functions are being carried out in such a coordinated manner, with so few disorders coming to the surface.

A large number of drugs may affect this organ in many different ways.

(a) Drugs may affect some of its vital functions—*secretory* and/or *excretory*, as in the case of choleretics and cholagogues, which affect the biliary functions.

(b) Being a most important detoxicating organ, practically for all the drugs and poisons, many of the drugs may act as hepatotoxic agents or *liver poisons*.

(c) There are other agents like lipotropic factors and drugs, which either prevent or ameliorate the fatty, infiltration or damage to the hepatic cells and are known as *liver protectives*.

Choleretics: These drugs which increase the production of bile, are the bile salts, salicylates and potassium salts. Alcohol and narcotics diminish the secretion. Bile salts are the most effective choleretics and are used in the form of *Extract of ox bile* (0.2—0.3 gm. tds). Besides being a choleretic, the bile salts also promote the absorption of fats and fat soluble vitamins and act as mild laxative. They are useful in chronic cholecystitis. They prevent ascending infections to the gall bladder by their 'flushing' actions. *Dehydrocholic acid* is used in the form of 'lecholin'—0.25-0.5 gm. tab/tds. L-phenyl propanol and florantyrone also possess choleretic action, the former, increasing both the volume and the constituents of bile, while the latter, only the volume.

Cholagogues: are the agents which cause contraction of the gall bladder and evacuation of bile. The most effective cholagogue is food and yolk of egg. Amongst drugs, oral magnesium sulphate is the best and it acts both on the musculature, as well as, on the sphincter of oddi, the sequence being—contraction of the sphincter and relaxation of the musculature, followed by relaxation of the sphincter and contraction of the musculature. Part of this action is also mediated through the production of *cholecystokinin*, in the upper part of the small intestine. For cholagogue action, magnesium sulphate is administered in a concentrated and flavoured solution in the morning, before breakfast, in a dose which does not cause any purgation.

LIVER POISONS

Because of the 'detoxicating function' of the liver and the chemical affinity of certain drugs, a number of substances are particularly toxic for this organ. The important hepatotoxic drugs are:

Halogens	Chloroform, carbon tetrachloride, alcohol
Metals	Arsenic, phosphorus, antimony
Synthetic compounds	Pyramidon, cinchophen, benzene and trinitrotoleone
Biological toxins	Malaria, kala azar, syphilis
Plant	'Senecio laifolia' producing cirrhosis of liver

In all such cases, the liver suffers from the limitation of a true hostess. Its recuperative power, however, is very great and it can readily regenerate itself even when a considerable portion has undergone damage. Some of these poisons are used as experimental tools for damaging the liver for evaluation of *liver protectives*.

LIVER PROTECTIVES

Besides the salutary role of carbohydrates on the liver, damaged by fats and poor nourishments, there are a number of agents considered to be protective against liver poisons. There are also other drugs which are frequently and effectively used in liver damage cases as adjuvants to the protectives. The important drugs for consideration in hepatic failure are—(a) glucose, (b) calcium gluconate, (c) liver extract, (d) vitamin B₁₂, (e) cortisone, (f) choline, (g) methionine, (h) glutamic acid, (i) neomycin, (g) vitamin K.

Lipotropic Factors: Fat metabolism is important not only from the point of view of source of energy but also of diseases involving liver and blood vessels e.g. fatty liver and atherosclerosis. The former is associated with deranged fat metabolism and the latter with abnormal cholesterol.

It was observed that experimental fatty liver could be prevented by *lecithin* and *casein*. The active principle was found to be choline in the former and methionine in the latter. These drugs which reduce the amount of fat in the liver are called *lipotropic factors*.

Choline and methionine possess labile methyl groups and can donate them to other substances through the process of transmethylation. Choline is the important 'lipotropic factor', while methionine is concerned more with the hepatic necrosis.

Choline: A simple quarternary NH_3 base and a member of the vitamin B complex, its daily requirement is 1.5-3.0 gms. This is readily available from the average diet and is absorbed from the G. I. tract, metabolised in the body and excreted in urine.

Actions: It is an essential constituent of phospholipid and lecithin, possessing lipotropic action for the fat and cholesterol transport. In the body, it acts as a methyl donor. Its deficiency causes renal injury, cardiac hypertrophy and hypertension, besides liver damage.

Preparation: chloride, gluconate and dihydrogen citrate salts, in the form of elixir, syrup, tablets and capsules. It is used in fatty infiltration of liver and cirrhosis, in doses upto 6 gms / day, along with high protein, and carbohydrate but low fat diet.

Methionine: It is sulphur containing essential amino acid, which donates the methyl radicle and acts as a lipotropic factor, preventing hepatic necrosis. *Dose:* 1.5-8 gm.

Inositol: A member of the Vitamin B complex and found in certain phospholipids. It partially prevents the fatty infiltration, induced by high cholesterol and biotin. As a lipotropic factor, it is less potent than choline and methionine.

Folic Acid: Besides its hoemopoietic effect, folic acid plays an important part in transmethylation, synthesis of choline and actions of methionine. Folic acid deficiency interferes with the lipotropic action of drugs and in this sense, it acts as a lipotropic agent.

Cyanocobalamine: Vitamin B_{12} plays a part in the synthesis of methyl groups and catalyses the transmethylation. B_{12} deficiency is a limiting

factor in the prevention of normal fat metabolism in experimental animals.

Certain other members of the vitamin B family also play a part in normal transport and metabolism of the fat, though their lipotropic effect are not so marked as of choline and methionine.

Lipocaic: It is a pancreatic extract, which prevents the deposition its choline content as also proteolytic enzymes which promote protein digestion.

THERAPEUTIC CONSIDERATIONS

Acute Hepatic Failure: It occurs in certain cases of infective hepatitis or in cirrhosis of the liver and is a very dangerous complication. In this condition, besides gross reduction in metabolic functions, other noticeable effects are—(i) reduced bile pigment excretion leading to jaundice and (ii) inability of the system to convert ammonia into urea. This causes derangement of the brain metabolism and neurological symptoms. The liver starts shrinking and there is receding of the hepatic dullness, increasing drowsiness and jaundice, which, in infective hepatitis, is preceded by excitement, restlessness and irritability. Coma ultimately supervenes and there may be unconsciousness, flapping tremors and bleeding.

The management comprises the following:

(a) In the early stages, intravenous glucose 5% drip, supplemented by 50% glucose. Large quantities have to be given so that the liver glycogen is restored.

(b) *Cortisone*: may act as protective and 'life saving' *Prednisol-one*—30 mg/day be given orally or in some injectable forms, like *dexamethasone*.

(c) *Sedatives* like paraldehyde 5 ml. I. M. or in the form of enema, is preferred to the barbiturates as it is little metabolised by the liver.

(d) Prevention of ammonia formation by destroying nitrogen forming intestinal flora with neomycin—2 gm/day and I. V. glutamic acid to neutralise ammonia by forming *glutamine*, may be tried.

(e) Finally, a broad spectram antibiotic for prophylaxis against infections and use of liver protectives such as choline, methionine—10-15 gm. may be tried, through often with doubtful prospects.

Hepatic Coma: Besides the above measures which are common to this as well, general management envisages:

- (a) Nutrition by I. V. route and maintenance of electrolyte balance.
- (b) Care of secretions from the respiratory passages and of the bladder and bowel.
- (c) Check up of prothrombin time, as its formation is often reduced resulting in bleeding tendencies. Administration of Vit. K-10 mg. I. M., if it is low.

In spite of all these, the ultimate outcome is generally fatal.

CHAPTER

39

PHARMACOLOGIC RESPONSES IN GASTRIC ACIDITY AND PLAIN MUSCLE SPASMS

ANTISECRETORY AND ANTISPASMODIC AGENTS. NATURE OF ACTION. ROLE IN HYPERCHLORHYDRIA AND PLAIN MUSCLE SPASMS

[Pharmacologic approaches to gastric hyperacidity, mostly comprises the uses of *alkalies* of different types; systemic or nonsystemic; absorbable or nonabsorbable buffer, certain antisecretory agents of atropine and atropine substitutes series—banthine, probanthine; enterogestron etc. In spite of many drawbacks, *sodabicarb* is still used as a short term therapy in acute hyperacidity states. As it is absorbable, it produces systemic alkalosis. *Aluminium hydroxide gel* is a good, nonsystemic preparation and has also astringent, demulcent and adsorbent properties. The same is the case with *magnesium trisilicate* which is frequently used in peptic ulcer. *Calcium* and *bismuth* salts are also nonsystemic and milder antacids but because of their astringent action, they tend to produce constipation and that is why, in *Sippy's Powder*, magnesium oxide is also added. *Enterogestron* is the physiological approach to hyperacidity and may be used more as a preventive than for cure. *Glycyrrhiza* or liquorice root combines demulcent, laxative, antacid, expectorant and also cortisone-like activity but its actual status has yet to be established. *Gastric mucin* is very occasionally used in combination with other antacids, in the form of *almagucin*, containing mucin, aluminium hydroxide gel and magnesium trisilicate and thus it cannot claim for an independent status.

The management of peptic ulcer also needs judicious use of some of the plain muscle antispasmodics. This group which includes coronary, bronchial, uterine and also gastrointestinal antispasmodics, have been studied in their respective chapters. However, in the management of intestinal, biliary and renal colic, as well as in spasm associated with peptic ulcers, drugs in common use are: *atopine* and *atropine-substitutes*: mydrindon, trasentin, pethidine, glyceryl trinitrate and other agents, some of which are also capable of reducing the secretion of hydrochloric acid in the stomach.]

The secretion of gastric juice, which besides the proteolytic enzymes, also contains the important constituent of hydrochloric acid, is modified in a number of conditions, the modification affecting either its excess as in acute indigestion and peptic ulcer or its deficiency, as in dyspepsia. It may be relative or absolute as observed in P. A. or in scirrhus cancer of stomach, respectively.

In cases of hyperchlorhydria, and also in G. I. irritation, there is increased spasms of the plain muscles, leading to colicky visceral pains. They have to be alleviated by the use of plain muscles antispasmodics, some of which also reduce the acid secretion of the stomach.

In this Chapter, it is proposed to study the following 3 groups of drugs: (a) Gastric Antacids, (b) Plain muscle spasmodics and (c) Antispasmodics. They are grouped together in view of their motor functions on the G. I. tract.

GASTRIC ANTACIDS

These are either alkalies, which directly neutralise gastric acidity or other chemical agents which by different mechanisms, like adsorption, ionic exchange or by changes in the secretory mechanisms, reduce the quantity of gastric acidity and are consequently used in cases of hyperchlorhydria. Their action, is mostly of the type of chemical neutralization and often palliative, though some of the members also act as protectives and demulcents, besides reducing the secretion of hydrochloric acid.

Secretion of gastric acid from the oxyntic cells of the stomach occurs in three phases. During interdigestive period, gastric acid is slowly and continuously secreted at the rate of 2.4 mEq/hour. This *basal secretion phase*, is blocked by anticholinergic drugs completely. The *neurogenic phase*, the nervous stimulation of sight, smell, taste or even thought of food and emotions like anger and resentment, excite, through vagus, the secretion of highly acidic and pepsin rich gastric juice. This phase is partially under the control of anticholinergic drugs. The above phase is followed by the *hormonal phase*, in which, gastrin secreted by protein food or gastric distention, stimulates oxyntic cells of the stomach, to secrete gastric hydrochloric acid. Gastrin secretion is inhibited by (i) low pH in the antral region, (ii) enterogastrone secreted into blood by duodenal mucosa and (iii) by gastrin antagonist—pentagastrin, 2-phenyl-2-(2-pyridyl) thioacetamide. All these are cyclically linked to one another, to meet with the need of gastric digestion. A normal stomach secretes about one litre or more of gastric juice per day, containing 0.35% of hydrochloric acid. The gram equivalent of pure hydrochloric acid, is about 3.5-5 per day, which can be neutralised by the following quantities of different substances.

Milk	1.5 litre.	Sodium bicarbonate	12 gm.
Magnesium oxide	3.0 gm.	Calcium carbonate	7 gm.
Magnesium carbonate.	7.0 gm.	Bismuth oxycarbonate	136 gm.

Classification: Gastric antacids are classified in a number of ways based on physical, chemical and pharmacological properties.

I. NON SYSTEMIC, NONABSORBABLE AND LOCALLY ACTING

- (a) *Buffer:* Aluminium hydroxide.
- (b) *Non-buffer:* Magnesium, calcium and bismuth salts.
- (c) *Physical Adsorbents:* Ion exchange resin, Mg. and Al. salts.

II. SYSTEMIC AND ABSORBABLE: Sodium bicarbonate, citrate and acetate.

III. HCl SECRETION INHIBITOR:

- (a) Cholinolytic Atropine and substitutes—Probanthine, Antrenyl.
 - (b) Ganglion Blockers—Hexamethonium, mecamlamine.
-

IV. HCl SYNTHESIS INHIBITOR: Acetazolamide (Diamox).

V. MISCELLANEOUS AGENTS:

- (a) Humoral: Urogastrone, Enterogastrone.
- (b) Pepsin antagonist—Amylopectin.
- (c) Gastrin antagonist—Pentagastrin.
- (d) Gastric mucin, Protein hydrolysate, Glycyrrhiza.

BIOCHEMICAL CONSIDERATIONS

The ionic composition of the gastric juice is H^+ and Cl^- ions. The former is obtained from the HOH and the latter from the extracellular fluid. The transfer of these ions to the gastric lumen leaves the blood concentration of Na^+ unchanged, chloride diminished and the bicarbonate increased. In the intestine, the bicarbonate is secreted more and in this way blood bicarbonate is brought down to the normal level, thus compensating for the changes produced by the secretion of the acid in the stomach. The interaction of the gastric HCl and the $NaHCO_3$ in the intestinal secretions occurs from sodium chloride and CO_2 . Sodium chloride is reabsorbed bringing the blood chloride concentration to the normal. Carbon dioxide is then absorbed in the circulation and is excreted by the lungs.

Systemic Antacid: If a systemic antacid, such as $NaHCO_3$ is taken orally, the HCl of the gastric contents is neutralised in the stomach and NaCl and CO_2 are formed. When the gastric contents pass into the duodenum, they require no neutralisation, with the result that the bicarbonate of the intestinal juice remains unchanged and is reabsorbed along with any excess of ingested bicarbonate, not neutralised in the stomach and sodium chloride formed. This leads to an increase in the bicarbonate concentration of the blood and a rise in pH. The kidneys

compensate this by excreting alkaline urine and if the renal mechanism fails, 'alkalosis' results.

Nonsystemic Antacid: When a nonsystemic antacid like MgO is given, it neutralises the gastric contents but does not cause systemic alkalosis. It reacts with the HCl in the stomach to form magnesium chloride. MgCl_2 reacts with NaHCO_3 in the intestine to form MgCO_3 , NaCl , H_2O and CO_2 . NaCl formed, is reabsorbed and the composition of the extracellular fluid is restored. MgCO_3 formed is relatively insoluble, poorly absorbed and therefore excreted in faeces.

Absorbent Antacids: They resemble the non systemic antacids in that they do not cause systemic alkalosis. The reaction in the stomach is physical, the HCl being simply absorbed. In the alkaline medium of the intestine, HCl is freed, neutralised and the formed NaCl , absorbed as usual.

Alkalosis: (a) The pH of extracellular fluid depends on the ratio of the carbonic acid and bicarbonate, the concentration of the former being regulated by the lungs and the latter by the kidneys.

(b) Increase in the concentration of BHCO_3 , causes a rise in the pH and is known as alkalosis. This may occur from the excessive ingestion of systemic antacids or failure of the kidneys to excrete NaHCO_3 , due to renal diseases, dehydration or haemorrhage. Alkalosis causes kidney damage and a vicious circle is established.

(c) Incidence of alkalosis in patients receiving systemic antacids is variously estimated from 8 to 40%. Death due to alkalosis with this therapy is sometimes unrecognised or attributed to other causes.

(d) Alkalosis is effectively treated by 0.9% NaCl I. V. In moderate cases of alkalosis, 10 mg. of NH_4Cl_2 may be given.

An Ideal Antacid: This is considered to be one which (a) does not cause systemic alkalosis, (b) does not produce rebound acidity, (c) causes less interferences with the digestive processes, (d) does not produce constipation or diarrhoea, (e) is non-irritant to the stomach, (f) does not release CO_2 (g) is efficient in neutralising acidity for a long time.

SODIUM BICARBONATE

(a) It is a short, immediately acting and fairly strong antacid, readily soluble and absorbable, producing systemic alkalosis (b) It liberates CO_2 in the stoma which may cause distension with consequent danger of perforation in case of peptic ulcer (c) It inactivates pepsin and retards the gastric phase of the digestion (d) It produces rebound acidity or secondary hyperchlorhydria (e) Dose—0.6-2.

Uses: Sodium bicarbonate has still a number of therapeutic uses and is probably the most popularly used antacid in current medical practice. It is used for the following conditions:

- (a) In systemic acidosis.
- (b) For immediate effect in gastric hyperacidity.
- (c) As a carminative.
- (d) As an alkaliniser of urine in any condition—ordinary fever, gout, renal calculus, cystitis and pyelonephritis.
- (e) In salicylate and sulphonamide therapies for minimising their renal toxicities.

ALUMINIUM SALTS

(a) In the stomach, aluminium salts combine with hydrochloric acid to form aluminium chloride (b) In the intestine the latter is converted to hydroxide or basic salts. (c) As they are not absorbed either from the stomach or the intestine, unlike sodium bicarbonate, they do not produce any systemic alkalosis or any other toxic symptom. (d) They effectively neutralise gastric acidity, inhibit peptic activity and reduce gastric secretions. (e) Being astringent, demulcent and adsorbent in action, they protect the ulcerated tissues from further damage and perforation and prevent intestinal toxæmia. (f) On prolonged use, they tend to cause constipation, which is counteracted by magnesium hydroxide, when used in combination.

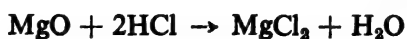
Preparations:

Aluminium hydroxide gel.	Liquid 8 ml., Tablet 0.6 gm.
Aluminium phosphate gel.	Liquid 8 ml.
Aluminium glycinate.	Tablet of 0.5-1 gm.
Mucotin tablet—containing gastric mucin, aluminium hydroxide and magnesium trisilicate, in quantities of 0.16 gm, 0.25 gm, and 0.45 gm. respectively.	

Uses: (a) Intestinal toxæmia. (b) Peptic ulcer. (c) Hyperacidity with adrenocortical steroids.

MAGNESIUM SALTS

Insoluble salts of magnesium are not absorbed in any significant quantity. They react with hydrochloric acid to form magnesium chloride.



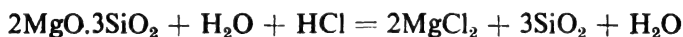
Magnesium chloride is soluble but the magnesium ion is not absorbed, Action is slow and prolonged and continued use may cause catharsis.

Preparations: Magnesium hydroxide or milk of magnesia and magnesium hydroxide mixture, are used. *Dose:* 4 ml. It is a mild antacid and laxative and is mostly used for children.

Magnesium Oxide: No carbon dioxide is formed during neutralization and it has more prolonged action than sodium bicarbonate. *Dose:* 0.25 gm.

Magnesium Carbonate: It acts like magnesium oxide, but liberates CO_2 . *Dose:* 0.6 gm.

Magnesium Trisilicate: It is hydrated magnesium silicate. $2\text{MgO} \cdot 3\text{SiO}_2 \times \text{H}_2\text{O}$. It is a non systemic antacid and a powerful adsorbent. It reacts with HCl to form magnesium chloride and hydrated silicon-dioxide.



Hydrated silicon dioxide formed, is of gelatinous, colloidal nature which forms a protective adherent coating over the ulcer. It also reduces the activity of pepsin by raising the pH and adsorbing the enzyme over silica gel and thus acts as a protective for ulcer. The antacid action is slow in onset but is prolonged and powerful. Its maximum action is during the first hour. It is one of the most useful drugs for relieving pain of peptic ulcer. It is also used as an adsorbent of toxins in intestinal toxæmia. Adsorption of fat and carbohydrate is not affected but that of protein may be slightly diminished. Large doses cause diarrhoea. *Dose:* 0.3 to 2 gm.

CALCIUM SALTS

The carbonate and hydroxide salts are used. Like magnesium, calcium salts are also converted to chloride in the stomach and are precipitated in the intestine as carbonate, producing constipation. Calcium carbonate liberates CO_2 , while calcium hydroxide does not do so and is very mild antacid. It acts as a protective and does not produce secondary hyperchlorhydria. *Dose:* 1-4 gm.

BISMUTH SALTS

Bismuth carbonate and subnitrate are used in the treatment of peptic ulcer. *Dose:* 0.6-2 gm. They are not strong antacids but protective

and demulcent. Bismuth carbonate forms a constituent of *Sippy's Powder*, the composition of which is as follows:

<i>Powder No. 1</i>	MgO and NaHCO ₃
<i>Powder No. 2</i>	BiCO ₃ and NaHCO ₃

The second tends to produce constipation and the first produces the opposite effects. By adjusting their proportions, the movements of the bowels can be kept in order.

ANION EXCHANGE RESIN

(a) Also known as *resinet* it is an insoluble and pharmacologically inactive substance, which given orally, acts as a non systemic antacid by adsorbing HCl in the stomach and releasing the same in the intestine, where it is neutralised. One gram of resinat is capable of raising the pH of 50 cc of gastric juice from 1 to 5. (b) The absorption is proportional to the surface area and therefore fine powder is preferred. (c) Resins are neither constipating nor cathartic and do not interfere with the intestinal absorption. (d) They are eliminated unchanged in the faeces. (e) They are available as powder, capsule or tablet. *Dose:* 0.05 gm/hr—first week; 2 hour per second week and thereafter.

ENTEROGASTRONE

It is a physiological approach to reduce gastric acidity and is used mainly for prevention, rather than treatment of peptic ulcer. In large doses given I.M., it induces hyperchlorhydria, due to histamine liberation. It also produces insulin hypoglycaemia.

GLYCYRRHIZA OR LIQUORICE ROOT

It is the dried rhizome and root of *Glycyrrhiza glabra*, and is available as brownish-yellow powder.

<i>Preparation:</i>	Extr. glycyrrhiza	0.6-2 gm.
	Extr. glycyrrhiza liq.	2-4 ml.
	Eulv. glycyrrhiza Co.	4-8 gm.

Action: (a) Given locally, it acts as a demulcent, while given internally, it is a mild expectorant. (b) It is also a popular vehicle and its protective and demulcent actions are being exploited for the treatment

of peptic ulcer with some benefit. (d) Of late, the plant has revealed fairly important cortisone like activity, particularly in Addison's disease, and has shown synergistic effect with it.

Uses: The drug is used for a number of conditions—(a) Demulcent in sore throat (b) Vehicle and excipient in pills and mixtures (c) Expectorant (d) Pulv. glycyrrhiza Co. which also contains senna, is used as purgative.

GASTRIC MUCIN

(a) Yellowish powder or granules obtained from the hog gastric mucosa by treating it with pepsin, HCl and alcohol. *Dose:* 2.5 gm/2 hourly. (b) It is a demulcent and antacid and possesses all the other properties of naturally secreted mucus. One gm. of gastric mucin neutralises about 15ml. of 0.1 NHCl. (c) *Experimentally*, gastric mucin has shown prolonged survival time in dogs with experimental peptic ulcer and reduced the incidence of ulcer formation after gastrojejunal anastomosis.

Its advantages are the lack of systemic alkalosis and minimal effect on the G. I. functions. The disadvantages are disagreeable salty taste and odour. It is used in combination with other antacids, as in, *Almagucin* containing gastric mucin, aluminium hydroxide gel and magnesium trisilicate.

Treatment of Peptic Ulcer: Peptic ulcer occurs mostly on the lesser curvature, pyloric antrum and within the first inch of the duodenum. The exact cause is not known but the condition is usually associated with hyperchlorhydria and mental stress and worries.

Its management comprises : (a) rest in bed, mild sedation and milk diet in the acute phase (b) Judicious use of antacids, antispasmodics and regulated regime with bland food, without roughage and spices. (c) The pain is partly due to the spasm and hypermotility. So, antispasmodics e.g. Tinct. belladonna or neotropin is helpful. In slightly large doses, they are also capable of diminishing the hydrochloric acid secretion. (d) Antacids, however, are the most important therapeutic measures for facilitating the healing of the ulcer and for affording symptomatic relief to the part. As numerous antacids are available, the choice is difficult. Before attributing greater credit to any particular compound, it should also be remembered that prolonged remissions are not uncommon in peptic ulcer and patients also show a less responsiveness to any drug used for a long time, thus necessitating the change of preparations from time to time. (e) Though many preparations are in actual use, as the clinicians have their own

- (i) Aluminium hydroxide gel.
- (ii) Aluminium dihydroxy aminoacetate.
- (iii) Magnesium trisilicate.

A large number of drugs produce spasms of plain muscles by a variety of mechanisms, central as well as peripheral, by acting either through the A. N. S. or directly (Plate XXXII). They include:

- In general, though all of them act on the plain muscles, their pattern of action varies according to the nature of functions of different systems and the type of the spasmodic used. Their action is quite often different on the smooth muscle of the cardiovascular system. Compared to those of other systems, for instance the parasympathomimetics and opium relax the plain muscle of blood vessels to effect vasodilatation, whole producing spasmogenic action on the G. I. T., R. T., G. U. T. and also biliary tracts.

ANTISPASMODICS

These drugs relieve the spasm of smooth muscles and are grouped according to the plain muscle, involved in their effect. They are used in

bronchial asthma, coronary disorders, intestinal, biliary, and renal colic and in peripheral vascular diseases.

The important plain muscle antispasmodics comprise : (a) coronary (b) Bronchial (c) Gastrointestinal (d) Biliary (e) Renal (f) Peripheral blood vessels and (g) uterine antispasmodic.

Coronary Antispasmodics: Nitrites, papaverine, theophylline, khelline, aminophylline. Their actions are direct and of muscletropic nature as already studied elsewhere.

Bronchial Antispasmodics: (a) Adrenaline, isoprenaline, ephedrine, arlidine. (b) Aminophylline, papaverine (c) ACTH and Cortisone (d) Antihistaminics. Their nature of action differs in different groups.

Gastrointestinal and Other Plain Muscle Antispasmodics: Belladonna, atropine and its derivatives and substitutes with parasympatholytic effect. The directly acting—papaverine, nitrites, calcium and magnesium and also volatile oils, possess plain muscle antispasmodic actions.

Peripheral Blood Vessel Dilators: Sympatholytics, nicotinamide, cyclospasmol, parasympathomimetic and ganglion blocking agents.

Uterine Antispasmodics: Lutrexin, viburnum, hydrastis and valeriana.

All these drugs have been studied in their respective chapters and their established therapeutic uses indicated. A brief mention will only be made about their uses in—(a) Intestinal, (b) Biliary and (c) Renal colics, at this place.

THERAPEUTIC USES

Intestinal Colic: This is a common condition affecting people of all ages from infancy to old age. In the mildest form, it may be the gripings of infants from milk clots and in adults from dietary indiscretion, indigestion, infection, appendicitis or an obstruction.

The line of treatment, in ordinary cases, comprises: (a) Rest to the digestive system and use of ordinary preparations like Gripe cure or a carminative mixture for children, (b) Judicious administration of an intestinal antispasmodic—(i) Tr. balladonna 0.3 ml t.d.s. (ii) Atropine sulphate 0.5 mg or (iii) Transentin 0.1 gm. tab. t.d.s.

The use of opiates is contraindicated before a correct diagnosis is made, for risk of masking the diagnosis of the underlying condition.

Biliary Colic: A cardinal symptom of lithiasis and cholecystitis occurring when a stone is lodged in the cystic or the common bile duct. The attack may be precipitated by dietary indiscretion or physical efforts. The pain in epigastrium gradually increases and spreads to the right hypochondrium. As a general principle, morphia is contra-indicated in biliary colic, due to its spasmogenic effect on the sphincter of oddi, but it is given in doss of 15-20 mg. S.C., repeated in one hour, if relief is not obtained with glyceryl trinitrate—0.5 mg sub-lingually, every 30-60 mins. In less severe cases, pethidine—100 mg. I.M., repeated after 2 hours, is recommended.

Renal Colic: A symptom of renal calculus which develops when a small stone enters the ureter and obstructs it. The pain increases in intensity and radiates to the groin testes or labia. The patient is restless and seeks for relief by frequently changing of position.

The treatment consists of: (a) Rest in bed and local application of heat, (b) Analgesics like morphine SO_4 —15-2) mg. S.C. or pethidine—100 mg., repeated once in 2 hours, (c) Antispasmodics—atropine SO_4 —1.0 mg. S.C., mydrindon or papavarine HCl-65 mg. I.V. (d) Sodium bicarbonate—4 gm. t.d.s. or citrates, (e) Plenty of fluids orally—3 lit/day, (f) Special preparations like *citralka* is also recommended for correcting the acidity of urine.

CHAPTER

40

DRUGS AFFECTING THE MOVEMENTS OF BOWELS

PURGATIVES, LAXATIVES AND ENEMATA USED IN INTESTINAL STASIS.
ASTRINGENTS AND INTESTINAL SEDATIVES USED IN DIARRHOEAS.
SCOPE AND LIMITATION

[The drugs which affect the movements of the bowels may either be (a) Purgatives or laxatives used for the treatment of constipation and intestinal stasis, for which last condition, enema are also sometimes used or (b) Astringents and intestinal sedatives, used for controlling irritation and diarrhoea.

The purgatives constitute essential domestic medication, often used and more often abused. There are various groups. The *lubricants* or emollients like liquid paraffin, soften the stool and act as a laxative or mild purgative. The *bulk cathartics* such as agar agar, which is hydrophilic, act by water imbibition. The salines act by drawing water by osmosis, the increased volume then stimulates the peristalsis. The stimulants and irritants are many. The anthracene cascara and senna, are mild purgatives, while aloes is more irritant. They all produce uncomfortable griping, controlled by antispasmodics. Castor oil and phenolphthalein also act by irritation, stimulating the peristalsis; the first cause after constipation and the second, prolonged effect for 2 or 3 days, due to its cyclic absorption and excretion from and into the gut, with bile. Croton oil, as well as drastic resins, cause violent irritation of small and large intestines and should preferably be not used.

Castor oil, salines and anthracenes are meant for occasional use in ordinary constipation accompanying fever or otherwise, in which, one day therapy is intended. For habitual constipation, correction of the diet habit with roughage, mild laxatives like isaphaghula, liquid paraffin, agarol, which do not irritate the bowels, are to be used. Saline purgatives are generally used during anthelmintic therapy and also sometimes in cases of hyperpiesis, uraemia and dropsy, but with appropriate precautions and care.

Enemata may be (a) evacuant, as in the case of soap sud enema or (b) retention, nutrient, astringent, sedative and antispasmodic. With the first, the rectum is unloaded and the second group is used for nourishment or medication purposes.

Astringents decrease the intestinal secretions, allay irritation and produce protective coverings over the surface of the mucous membrane. They may be metallic or vegetable, the latter comprising tannic acid containing substances—kramaria and catechu. Bismuth salts, kaoline and chalk are also used for this purpose. For the management of diarrhoea, beside drugs like sulphonamides and streptomycin, for dealing with the infective conditions, an initial dose of purgative, followed by the use of demulcants, absorbants, sometimes opiates, essential oil mixture and also belladonna antispasmodics, are used.]

PURGATIVES

General Considerations: The 'humoral school' of the 18th century believed in the origin of all diseases from blood impurities and prescribed (a) emetics, (b) purgatives and (c) venesection, as corrective measures.

Though these crude conceptions have since been rejected, there is still scope for improvement in the uses and abuses of purgatives.

Since the work of Alvarez and Hurst, it has been established that there is no place for irritating, drastic purgatives in therapeutics and only non-irritating, laxative aperients, should be used with benefit, in selected cases of intestinal stasis.

Further, besides the different types of intestinal movements, other factors of importance, associated with the regular evacuation of bowels, which should be borne in mind, are (a) General health and status of the intestinal muscle (b) Regular habit for utilising the mass reflex of the colon which is a conditioned reflex and (c) Quantity, nature and quality of intestinal content for keeping the gut in optimum irritability for evacuation. All these factors combine together to constitute regular motions and the laxatives and aperients only, can remedy some of these defects partially and palliate the conditions.

Laxatives or aperients: They increase the peristalsis moderately but the number and the consistency of the stool remain within the normal range i.e. not exceeding 2 motions of semisolid consistency per day. There is no marked irritation of the gut produced by these drugs.

Purgatives or cathartics: They increase the peristalsis considerably. The stool is fluid, frequency greatly increased and there is certain amount of irritation of the gut, associated with their use.

CLASSIFICATION

<i>Lubricants</i>		<i>Liquid paraffin, olive oil</i>
BULK CATHARTICS	Colloidal	Agar-agar, psyllium seeds, tragacanth, sodium alginate, methyl cellulose, gumacacia, sodium carboxymethyl cellulose, bran, figs, prunes.
	Saline	Magnesium sulphate, oxide and citrate, sodium sulphate, sodium and potassium tartrate.
STIMULANT OR IRRITANT CATHARTICS	Anthracenes	Cascara sagrada, senna, rhubarb, aloes, phenolphthalein.
	Resins	Colocynth, jalap, podophyllum, ipomoea.

The salines and resins are also known as *hydrogogue purgatives*. The resins and croton oil as *drastic purgatives*; the anthracenes and mercurials as *cholagogue purgatives*, pilocarpine, doryl, prostigmine and also pituitrine and thyroid as *hypodermic purgatives* and the first three also as *neurogenic purgatives*.

- Modes of Study:** (a) Isolated and *in situ* intestine of rabbit.
(b) Quantitative estimation of stool in animals
(c) X-Ray evaluation with barium meals.
(d) Clinical trial in which quantity, frequency, consistency and side-effects, are noted.

LUBRICANTS

Liquid Paraffin and Olive Oil: They lubricate and soften the stool and act as mild laxatives. *Dose:* 15-30 ml.

These oils are unabsorbable and the first undigestable. They lubricate the contents of the colon and prevent dehydration of stool. They are partially emulsified in the intestine and also hold some water. They disturb the absorption of food, as well as fat soluble vitamins. They are taken at bed time and are disliked by patients. As they are non-irritant, they are suitable for chronic constipation and colitis. They, however, disagreeably leak through the anus and this is very annoying to the patient.

COLLOIDAL HYDROPHILIC BULK LAXATIVES

The group contains gelatinous, colloidal substances, which in contact with the intestinal moisture, swell up and the increased bulk stimulates the peristalsis mechanically. They are slow and mild in action, non-irritating and can be used frequently with impunity.

Agar-Agar: A gelatinous substance, extracted from Japanese or Chilka lake mosses. It is available as shreds or powder, soluble in boiling water, setting into jelly on cooling.

Petrol agar, agarol—*Dose:* 4-16 ml. They take about 10-12 hours for producing evacuation and are to be taken at bedtime.

Cassia Pulpa: It is obtained from the cassia pods. *Dose:* 4-8 gm. and is used with 'confectio sennae' for preventing griping.

Manna: It is an exudate of *fraxinus ornus*, containing mannitol. In 1-16 gm doses, it is used as a mild laxative for children.

Ispaghula: A mucilaginous substance, obtained from *Plantago ovata*. The seeds are soaked in water and the mucilage taken next morning. **Dose:** 15-60 ml. It is a good demulcent and laxative and popularly used in chronic constipation and colitis.

Methyl Cellulose: In doses of 1—1.5 gm., it forms a colloidal solution in the upper gut and having lost water in the colon, it forms a gel, which by increasing the bulk of the stool, acts as a laxative. It is a partially polymerised colloid and is dispensed as tablets, granules, or powder. It is neither digested, nor absorbed. Sodium sulphomethyl cellulose also acts in a similar manner.

Acacia and Tragacanth: The former is almost entirely soluble forming a mucilage, while the latter, which contains also bassora, is partially so. The insoluble fraction imbibes water, swells up and acts mechanically producing bulky, soft, formed stool. These gums may sometimes give side effects of impaction.

Bran and Dried Fruits: also act as cellulose and roughage. They should not be used in inflammatory conditions.

Diocetyl Sodium Sulphosuccinate: A wetting agent which allows water to penetrate the faeces. It is used in 1% solution with fruit juice, in doses of 2 mg/Kg. It thus acts as a 'foecal softener' in chronic constipation.

SALINE BULK CATHARTICS

These retain fluids in the intestine, stimulate persistalsis and produce purgative action in 3-4 hours, sometimes even earlier, due to the colonic reflex after entry of hypertonic saline in the small intestine. The important members are:

<i>Salts</i>	<i>Preparations</i>	<i>Dose</i>	<i>General remarks</i>
Magnesium	Magnesium sulphate (Epsom's salt)	2-16 gm.	They act locally on the small intestine by changing the osmotic pressure of the fluids.
	Mist. magnesii hydroxide	4-16 ml.	
Sodium	Sodium sulphate (Glauber's salt)		At 6.5% they are isotonic in the intestine and at 8% concentration, they retain 120 ml. of water.
	-do- effervescens	4-16 gm.	
	Sodium phosphate -do- effervescens		

<i>Salts</i>	<i>Preparations</i>	<i>Dose</i>	<i>General remarks</i>
Sodium and Potassium	K and Na tartrate— (Rochell salt) Pulv-effervescens co. (Seidlitz powder)	8-16 gm.	They are little absorbed from the gut and if absorbed, they produce diuretic action. They are taken in the morning as an aperient. Their purgative action is due to the anion or cation or both.

Of these, magnesium oxide and carbonate act mostly as antacid and the former, as mild laxative also. However, magnesium and sodium sulphate act as potent purgatives, while sodium phosphate and *Seidlitz powder*, act as aperients.

Magnesium SO_4 : (i) Colourless, freely soluble and very efficient purgative, (ii) Both the ions resist absorption and in 15 gm doses, can retain about 400 ml. of water in the intestine, (iii) Mg. ion is toxic and if absorbed in sufficient quantities or after injection, may produce anaesthesia, specially, if the kidney functions are impaired.

Sodium SO_4 : (i) As effective as MgSO_4 , if not more so. (ii) In 15 gm. doses, it retains about 500 ml of fluid. (iii) Though much less toxic, because of worst taste, it is less frequently used.

Sodium phosphate: (i) A pleasant purgative but less powerful than the sulphate compounds, (ii) In effervescent form, containing also tartaric acid and sodi bicarb, it is more palatable than sodium phosphate itself.

Potassium sodium tartrate: (i) It is freely soluble and not unpleasant in taste, (ii) The 'Compound effervescent powder' or 'Seidlitz powder', (containing NaHCO_3 , Na and K tartrate—in 1 packet and tartaric acid in another), is popularly used as a domestic aperient, in doses of 10 gm.

Mode of Action: All the saline purgatives act by disturbing the osmotic balance in the intestine. As a result of this, fluid is not absorbed in the gut and if hypertonicity is produced, water is drawn from the intestine. The bulk in the intestine stimulates peristalsis and hastens the exit like an enema.

Uses: (a) Constipation of an acute nature accompanying fevers, (b) Reduction of body weight and B.P., (c) Expulsion of ingested bad

food and poison, (d) Relief of portal congestion and (e) Treatment of bacillary dysentery, along with sulpha drugs.

They usually act quickly and are taken in the morning in the empty stomach. As they produce distension of bowel, they should be used occasionally and not as a regular feature.

STIMULANT OR IRRITANT CATHARTICS

Of the two irritant oils—croton, containing a drastic principle, will be studied with that group and only castor oil will be discussed here.

Oleum Ricini: It is obtained from the 'Ricinus cominunis' or castor seeds. It is a triglyceride of ricinoleic acid which is the purgative principle. *Dose:* 4-16 ml. It is used in frequent doses, mostly in the form of emulsion—8 ml./OS, as a mild purgative.

Action: The oil is bland and soothing for the eye and the mucous membrane. It is also used as a hair tonic. It behaves like any oil in the stomach but in the duodenum, it is saponified and converted to glyceriol of sodium ricinoleate and ricinoleic acid, which acting as irritants, stimulate the peristalsis and hurry the fluid into the colon, producing few copious, semifluid stools, within 3-4 hours without much griping. The unsaponified oil softens the faeces and lubricates the tract.

Uses: A safe purgative for children and old people in acute constipation after dietetic errors and also for piles, fissures, indigestion and during labour.

It relieves portal congestion and is also used in dysentery. The oil produces *after constipation* and is therefore unsuitable for the treatment of chronic constipation.

MISCELLANEOUS IRRITANTS

Phenolphthalein: Yellowish-white, insoluble tasteless and odourless powder, chemically belonging to the *anthraquinon group* of purgatives. *Dose:* 15-75 mg. A pleasant cathartic which is included in the proprietary preparation *castophen*.

Action: (a) It has a cyclic absorption, excretion and reabsorption from and into the intestine through the bile, thus producing *prolongation of purgative effect*.

(b) It is dissolved in the duodenum in the alkaline medium in the presence of bile. In soluble form, it irritates the small and the large intestine and produces purgative effect in 4-8 hours, without griping.

(c) About 15% is absorbed into the circulation and the rest excreted in the faeces. The absorbed fraction is excreted through the kidney, in combined and free forms. The free form colours the urine red, if the latter is alkaline.

Toxicity: In hypersensitive persons it may induce (i) excessive purgation, colic and collapse, (ii) polychromatic skin rashes with itching, (iii) dermatitis and pigmentation of the skin.

Phenolphthalein is a simple purgative, used as tablets, in debilitated persons and also as a domestic drug but as it acts as an intestinal irritant and is not free from toxicity, it is better not to use it as a routine purgative.

Calomel: or HgCl or mercurous chloride is an insoluble salt and once a popular remedy for biliousness: *Dose:* 30-180 mg.

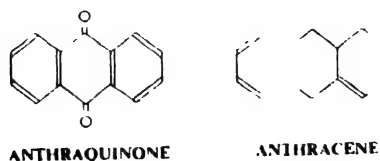
Action: (a) In the alkaline intestine, in the presence of bile, it is partly converted to the insoluble mercuric oxide. The mercuric ion is irritant and produces cathartic action. The insoluble portion is excreted in stool. A small fraction enters into the circulation, if elimination from the bowel is retarded. This may produce diuretic effect.

(b) Choleric action has not been demonstrated by the biliary fistula and its cholagogue action is also doubtful. The greenish stool may be due to the antiseptic action of the drug in intestine and thus biliverdin is not converted to bilirubin.

Calomel acts better in repeated, fractional doses, followed by a 'saline purgative'. It shows a definite colonic exit in about $3\frac{1}{2}$ hours and the purgative action in 4-5 hours.

ANTHRACENES

Aloes, senna, rhubarb and cascara belong to this group of stimulant irritant purgatives. They all contain glycosoidal bodies of the type of *hydroxy methyl anthraquinone derivatives*. Emodin, trioxymethyl anthraquinone, chrysophanic acid, dioxymethyl anthraquinone, are present in these plants. Anthracene, $C_{14}H_{10}$ and anthraquinone, $C_{14}H_{8}O_2$ are represented by the following formulae.



Illustr. XXI: Basic nuclei of anthraquinone and anthracene

The activity of anthracene purgatives is mostly due to *emodin*, which is slowly liberated from the preparations in the large intestine for producing the purgative action. The delay in the production of the purgative action is due to (i) its absorption from the small intestine and re-excretion in the colon, the irritant effect being produced on both, (ii) it takes 6-10 hours to reach the large intestine which is its main site of action.

Aloes: Socotrine or Zangiber aloes grows in Africa. *Dose:* 120-300 mg. The dried juice of the leaves is dark brown in colour and contains a mixture of glycosides, aloin. It is a micro-crystallin lemon-yellow powder of bitter taste. It is hydrolysed in the intestine to produce the purgation, as well as its worst griping and pelvic congestion.

Preparations: Extract 60-240 mg.
Aloin 15- 60 mg.

There are also a series of pills—pil. aloes; pil. aloes *et ferzi*, and pil. aloes *et asafoetida*. *Dose:* 240-480 mg.

Rhubarb: The dried rhizome of *Rheum officinalis* grows mostly in Tibet and China. This variety is not edible. The active principle is known as 'rhein', a dioxycarboxyanthraquinone. It causes griping and also the colouring of urine.

Preparations: Pulv. rhei Co. (Gregory's powder) — 0.6-4 gm.
Tinct. rhei Co. — 2-4 cc. ml.
Pil rhei Cò. — 240-480 mg.

Senna: The dried leaflets, as well as pods of *Cassia angustifolia* and *C. acutifolia* growing in Alexandria and America are used. *Dose:* 0.6-2 gm.

Sennosides, which are the active principles, are mostly used as laxatives and have very little side-effects of griping.

Preparations: from the folia, powder, confection and pulv. glycyrrhiza Co. and from the pods, powder, extract, syrup and mist. senna Co. are prepared.

Powder	0.6 - 2 gm.
Confectio and Pulv. glycyrrh. Co.	4 - 8 gm.
Extract and syrup	1 - 4 ml.
Mistura senna Co. (black draught)	15-30 ml.

Cascara Sagrada: The dried, sacred bark of *Rhamnus purshiana*, grows in U. S. A. and Canada. The fresh bark is irritant but on aging for 1 year, it develops the required emodin, resin, tannin and the bitter principle. The emodin content is 2%. *Dose:* 1-4 gm. It does not

produce any secondary constipation nor any irritation and is the best and mildest of the lot.

Preparations: Liq. Extract and Elixir : 2-4 ml.
Tablets. : 200-400 mg.

ANTHRACENES COMPARED

<i>Drugs</i>	<i>General actions</i>	<i>Special actions</i>	<i>Indications</i>
ALOES	(a) All contain emodin, which is split up in the large intestine slowly producing purgative effect in 6-10 hr.	Congestion of pelvic organs and griping. C. I. menses, pregnancy and haemorrhoids.	Constipation Amenorrhoea with anaemia & debility. Use restricted because of irritating properties.
SENNA	(b) All produce some amount of griping which can be counteracted by belladonna. Cascara has it the least, senna next and aloes the most.	Some griping and pelvic congestion but no secondary constipation.	A harmless cathartic for constipation of pregnancy. Infusion acting better.
RHUBARB	(c) Most of them turn urine yellow due to presence of chrysophanic acid.	Maximum griping and secondary constipation, because of high tannin content. It has also stomachic action.	A nursery remedy for mother and the baby. Excreted through the milk.
CASCARA		Least griping but also stomachic, aperient and laxative actions. No secondary constipation, nor tolerance.	Best in the group, and useful for habitual constipation.

DRASTIC RESINS

They comprise (i) jalap, (ii) podophyllum, (iii) colocynth, (iv) croton oil, (v) ipoeimia. The active principles are 'resins' of glycosidal nature, which are violently irritant for the small as well as the large intestines, producing nausea, effusion and tenesmus.

Normally, the crude resins are slowly split into the irritating principles and are considerably diluted in the intestinal fluid and hastened through the intestine. Otherwise, as in cases of intestinal obstruction, they can produce inflammation and paresis of the gut.

Jalap: The dried tubercles containing 9-18% of resin, is responsible for the pronounced irritant and hydragogue effect of the drug. The active principle is supposed to be jalapine.

Pulv. Jalap	0.3-1.3 gm.
Pulv. Jalap Co.	1.0-4.0 gm.

Colocynth: The pulp of the bitter apple, containing an amorphous resin and a purgative alkaloid—'colocynthine'. It produces marked irritation of the G. I. tract with violent peristalsis, congestion of the pelvic organs and even abortion.

Ext. colocynth Co.	: 150-300 mg.
Pillula colocynthi et hyocyanus:	100-400 mg.

Croton Oil: An irritant oil, containing the purgative resin, obtained from *Croton tiglium*. It is irritant both for the skin, as well as, the mucous membrane and produces copious watery stool, even from one drop dose, placed on the tongue on a lump of sugar. *Dose:* $\frac{1}{2}$ -1 drop only.

Podophyllum: The resin is extremely irritant and is supposed to have some cholagogues effect also. The drug may induce vomiting, severe purging, prostration and even collapse. The cytotoxic action of this drug is interesting and it is capable of inducing mitotic changes in the cytoplasm and the nuclei. This effect is attributable to podophylotoxin. *Dose:* Podophyllum resin: 60 mg.

Ipomoea: The Mexican scammony and very similar to jalap in action. *Dose:* Resin 30-180 mg.

In substance: None of the resins has any place in therapeutics. Of the 6 members, jalap is the mildest hydragogue, podophyllum and ipomea—slowest but also possessing hydrogogue and cholagogue actions in biliousness, colocynth and croton oil—most irritant, the former being used in ascites and the latter, in view of drop doses, in apoplexy and coma. In practice, their uses have completely been abandoned now.

X-RAY ANALYSIS OF ACTION

	Normal Hrs.	Mg. sulph. 2 hrs. after Bismuth Hrs.	Castor oil with Bis- muth meal Hrs.	Senna infusi- on after Bis- muth meal Hrs.	Colocynth infusion with Bismuth meal Hrs.
Maximum shadow.	4	2	2	4	1.5
Emptying of the small intestine.	10	5	5	10	4
Entrance of meal in the caecum.	5	2.5	2	6	1.5
Defaecation.	24	4.3	4.5	6.5	1.5-4.0

SITE AND TIME INTERVAL IN HOURS OF ACTION

Emollient laxatives.	Small and large intestine.	12-16
Castor oil.	Small intestine.	2-4
Calomel.	Both intestines.	3-4
Salines	Both but small intestine. particularly.	2-4
Sennosides.	Large intestine mostly.	6-10
Resins.	Mostly small but large also.	1-2

ASTRINGENTS

The term 'astringent' refers to the binding and arresting of secretions by a group of drugs, which, by acting locally on the skin and mucous membrane, produces the following typical actions at different stages; (a) Hardening, retraction and roughening of tissues. (b) Precipitation of protein and formation of protective layers. (c) Local anti-inflammatory and antisecretory actions.

They are not absorbed through the G. I. tract and act locally in diarrhoea as protective for irritated mucosa making them useful for the management of diarrhoea.

Classification: Two types:

- (a) *Vegetable:* Tannic acid and tannic acid containing substances—catechu, rhatany and kino.
- (b) *Metallic:* Pb, Ag, Cu, Zn, Alum, Bi, Chalk and Kaolin.

VEGETABLE ASTRINGENTS

Tannic Acid: It is prepared by the fermentation of gall nuts and is a brownish-yellow scaly powder of astringent taste, the aqueous solution precipitating alkaloids. *Dose:* 300-600 mg.

Actions: They implicate skin and mucous membrane, thus affecting the G. I. tract also.

On the G. I. tract, the typical astringent action, referred above, is produced. Catechu acts better than tannic acid as tannic acid is slowly liberated and the action is more prolonged. On the intestine, the action consists of: (i) precipitation of food protein, (ii) protection of mucous membrane from irritation, (iii) decreased secretion and (iv) slow expulsion leading to constipation.

- Preparations:* (a) Glycerinumacidi tannici : 15% as throat paint.
 (b) Suppository : 0.2 gm. each — for piles and rectal hæmorrhages.

Uses: Tannic acid is used for:

- (a) Hardening of nipples.
- (b) Treatment of burns— (10% sol. sprayed every 15 min. till mahogany colour, combined with 1 in 1000-acriflavine). It leaves unsightly scar and its use has been discarded now.
- (c) Antidote for poisons and
- (d) Diarrhoea.

Catechu: An extract of *Uncaria gambier*, containing 36% of catechu tannic acid. It is of dark brown colour and characteristic taste. *Dose:* 5-15 gm. *Tinct. catechu:* 2-4 ml. It is an intestinal astringent and sometimes included in the *Chalk Mixture*, used in diarrhoeas.

Kramaria: or *rhatany root*: *Dose:* 0.6-2 gm. *Tinct. kramariae*— 2-4 ml. *Use:* (a) Intestinal astringent, (b) Mouth wash.

Kino: 0.3-1 gm. *Pulv. kino Co.*, containing opium; *Dose:* 0.2-1.3 gm. It is an intestinal astringent with longer and more lasting action.

Hammamelis: *Ointment:* 10% is used as an astringent and haemostatic in piles.

METALLIC ASTRINGENTS

Insoluble salts of calcium, bismuth, and kaolin are used in the form of finely divided powders or mixtures. They are protective, non-absorbable, nonirritant and adsorbents of toxins and moisture.

Bismuth Salts: They include carbonate, subnitrate, salicylate, subgallate and aluminate, which act by covering the gastro-intestinal mucosa with an adhesive coating, producing protective and soothing effect on the inflamed, irritated and ulcerated surfaces. They are used in the treatment of peptic ulcer, gastritis and diarrhoea. *Dose:* 0.6-2 gm.

Kaolin: It is a purified form of aluminium silicate and is used as an adsorbent and protective for symptomatic relief of dysentery, gastroenteritis and diarrhoea.

Calcium Carbonate: It is converted to chloride in the stomach and is precipitated as carbonate in the intestine, where it produces its consti-

pating action. This property is made use of in the well known *Chalk and opium mixture*. This, as well as, *Bismuth-kaolin mixture* are used in diarrhoea, as a palliative measure.

ENEMATA

This actually refers to the administration of drugs and chemicals through the *rectal route* for local, mechanical or systemic actions. Accordingly, there are two types of enemata in use:

1. Evacuant enema
2. Retention enema

The *first* is intended for unloading the contents of rectum by mechanical stimulation of rectal wall by increased hydrostatic pressure or by softening the faecal matter for easier expulsion. The *second* is meant for local, as well as, systemic action and also for supplying nourishment to the patient after absorption.

1. Evacuant Enema: In certain conditions like chronic constipation, Hirschprung's disease etc., the regular evacuation of the bowel does not occur causing discomfort to the patient from impacted scybella and accumulation of gases. In certain cases, masses of thread worms also cause similar troubles. In such cases, unloading of the rectum and relief of symptoms can be effected by the following devices:

(a) *Softening enema:* Olive oil, glycerine, ox bile, mucilage and starch, introduced with a rectal syringe, soften hard stool and permit evacuation of the bowel in a gentle manner.

(b) *Cleansing enema:* In this, soap water from few millilitres to half a litre, depending on age, is introduced into the rectum for evacuation purposes. Sometimes, *quassia infusion* and *hypertonic saline* are also used in small quantities for removing thread worms from the rectal passages.

(c) *Gas expulsion enema:* It consists of soapsud with 15 ml of turpentine oil litre, which is used for expulsion of flatulence and relief of associated discomfort.

2. Retention Enema: In this, a drug is introduced into the rectum for therapeutic purpose, in the form of a solution, intended either for local or systemic action for absorption without causing evacuation. Several important drugs, as well as, some of the nutrient fluids are conveni-

ently administered to comatose or debilitated patients in this manner. The important ones are detailed below:

(a) *Nutrient enema*: The colon can absorb about 0.5-1 litre of water, some salts and also glucose. Ordinary proteins, fats, peptones, milk, egg albumin are not absorbed from this route. *Glucose*—75 gm. in a 5-10% solution at 98°F, is sometimes used as a nutrient enema and this quantity can provide about 300 calories to the patient. Similarly, protein hydrolysate 200-300 ml. or more is administered for nourishment of debilitated patients, by the rectal route.

(b) *Astringent enema*: Containing tannic acid and hamamelis are sometimes used for alleviating local inflammations and haemorrhoids.

(c) *Sedative enema*: *Tincture opii*, with mucilage and starch, is used for sedation and relief of painful conditions. Similarly, *Paraldehyde* is frequently used for its hypnotic action through the intrarectal route.

(d) *Antispasmodic enema*: Several drugs, including turpentine and bromides, are used for producing antispasmodic action in patients, provided that, they are satisfactorily absorbed by this route.

The scope of use of therapeutic enema is no more limited and the essential prerequisites are that the substance used is not only non-irritating but is also absorbed sufficiently to produce effective systemic concentration, for initiating drug action. Besides their local action, they are useful in non-cooperative and unconscious patients in whom it may be difficult to administer drugs by the oral route.

SUPPOSITORIES

These are conical medicated preparations containing theobromine base and meant for insertion into the anal canal where they melt at body temperature, lubricate the passage and produce their local action. There are several of them, of which, the following are commonly used:

(a) *Glycerine suppository*: It is used for moving bowels in cases where purgatives are contraindicated e.g. typhoid fever.

(b) *Tannic acid suppository* is used for local astringent and haemostatic actions.

(c) *Mercurysuppositories* are also available for rectal use as diuretics. Similarly, *aminophylline* may also be used per rectum for antispasmodic effect.

AUTO INTOXICATION

A number of protein breakdown products—histamine, tyramin, skatol and indol, are formed in the intestine from fermentation and stagnation. Due to rapid transit, normally they are not absorbed to any appreciable quantity from the small intestine and are not absorbed from the large intestine, as only water can be absorbed from there. In cases of intestinal stasis in habitual constipation, irritation of intestine from diarrhoea or from frequent uses of purgatives, their absorption may be facilitated. In liquid stool, bacterial activity is also accelerated, leading to the formation of these bodies. Normally, the liver cells deal with their detoxification but when it cannot be appropriately done, signs of auto-intoxication with vague symptoms of morning headache, malaise, bad mouth and disinclination for getting up from the bed, occur.

Management: Though the theory of auto intoxication has virtually been discarded, the symptom-complex is still there and has to be dealt with in a large number of cases, with some of the following lines of therapeutic measures:

(a) Attention to regular bowel habit by use of mildest, non-irritant, laxative and occasional saline, washing out the toxin, if need be.

(b) Use of calomel, salol, naphthol and other intestinal antiseptics, though of very doubtful value, in the present concept of their efficacy.

(c) Periodical use of kaolin adsorbent when the bowels tend to be loose.

(d) Correction of underlying infections, with specific chemotherapeutic agents of sulphonamide and oxyquinolene series according to the nature of infection detected.

(e) Vitamin supplements to make good the deficient work of vitamin synthesis by the intestinal flora.

(f) Improvement of general health by simple food, rest, recreation, light exercise and also use of digestive enzymes, as in the cases of dyspepsia.

THERAPEUTIC CONSIDERATIONS

The functions of the G. I. tract and actions of drugs on this and accessory systems are complex. There are conditions in which an approach with specific therapy produces a marvel, while in others, all efforts, to the most, produce only some palliation or symptomatic relief. Conditions like amoebic and bacillary dysentery, typhoid fever, intestinal tuberculosis, will be dealt with in their respective chapters. Manage-

ment of two general conditions—(a) *Constipation* and (b) *Diarrhoea*, which need the use of purgatives and astringents respectively, along with other measures of therapy, is detailed hereafter:

Constipation: The concept of periodic uses of purgatives to overhaul the system, use of preliminary purgatives in all cases of fevers and infection, potent purgatives given before anaesthesia and delivery, has undergone radical changes. It is now believed that they should be used only when essentially needed and that also by selecting cases and drugs carefully. This is because the purgatives produce—(a) secondary constipation, (b) disturbance in the normal biosynthetic activities of the intestinal flora, (c) debilitating effect on the patients and (d) also because of the availability of specific drugs for intestinal organisms. A mild degree of constipation is not incompatible with normal health and should not be allowed to preoccupy the mind of patients too much.

The conditions in which laxatives and purgatives may be indicated are:

(a) *Constipation accompanying acute fevers:* Occasional use of castor oil, salines and anthracenes may be advocated.

(b) *Ordinary constipation:* Cascara, phenolphthaline and senna, may be prescribed.

(c) *Habitual constipation:* Correction of diet, roughage, fruits and mild laxatives: Isphaghala, liquid paraffin, agarol and occasional anthracenes, may be used.

(d) Purgatives are generally used before and after administration of anthelmintics.

(e) In hyperpiesis and uraemia, hydragogue purgatives: salines and pulv. jalap co. may be occasionally tried when other measures fail.

Purgatives are usually contraindicated in cases of intestinal obstruction and inflammation. Drastic purgatives are not to be used during pregnancy and menstruation and in cases of debility.

Diarrhoea: Like vomiting, it is often a protective reaction but left alone, in cases of serious infection, can produce far-reaching complications in the old and the young alike. Besides the local irritation, the underlying infection should always be attended to, as a curative measure.

For management of diarrhoea, the following general measures may be considered:

(a) In cases of irritation and toxin, castor oil or magsulph purgative for exonerating the intestine may be recommended.

(b) *Absorbents and demulcents*: Charcoal, kaolin, chalk, 4 gm. each, may be prescribed in early stages.

(c) The opiates in the form of paregoric, pulve cretae cum opii, chlo-rodyne, have long been in use and are still sometimes used.

(d) Essential oil mixture, as used in the treatment of cholera in the past, because of the astringent and antiseptic actions, has lost its grounds completely in recent years.

(e) Belladonna, hyoscyamus and other intestinal antispasmodics are used for the relief of griping, associated with diarrhoea.

(f) In infective conditions, with pyrexia, sulpha drugs—sulphaguani-dine, sulphadiazine, sulphathaladine, antibiotics—streptomycin, aureo-mycin, terramycin, and in cases of underlying amoebiasis, enterovio-form and other amoebicidal drugs are to be used.

It may however, be argued whether, in the light of recent advances, all these elaborate measures of treatment could still have some places in modern therapeutics. The old, founded on years of observation, could still be useful in many ill-defined conditions in which costly drugs may not have any special advantages over the older ones.

CHAPTER

41

PHARMACOLOGY OF ANTHELMINTIC DRUGS

INTESTINAL AND TISSUE HELMINTHS. LIFE CYCLE AND MODE OF INFESTATION. STATUS AND LIMITATIONS OF DRUG THERAPY

[There are two principal types of helminths infesting the human systems (a) Intestinal and (b) Tissue Worms. The anthelmintics act either by killing them as *vermicides* or by helping in their expulsion, as *vermifuge*. These worms cause trouble to the patients by robbing them of their nutrition, mechanical injuries and obstructions, colic pains, urticaria and eosinophilia.

For tape worm, mepacrine is the drug of choice. For round worm—piperazine and hetrazan. For hook worm—tetrachlorethylene and alcopar and for threadworm—piperazine and gentian violet. For whip worm—cyanine dyes and for strongyloidosis—gentian violet are used. So far as filaria is concerned, the drug of choice is hetrazan and for guinea worms—streptomycin.

The management of worm infestation is often complex, involving preparation of patients in tape worm infection, administration of drugs in divided doses at short intervals and use of purgatives before and after drug therapy. Regular stool examinations for the presence of ova is to be carried out and chances for re-infection ruled out. In cases of hook worm, the associated anaemia should be treated and in cases of superinfection broad spectrum anthelmintic effective against the infective parasites, preferred.]

Worm infestation is one of the greatest scourges in our society, the number of infestations being in excess of the world population, due to the incidence of *super infestation*.

These worms, which belong to two distinct categories, (a) intestinal and (b) tissue helminths, like true parasites, undermine the health of their victims in various ways.

(a) Robbing the hosts of nutrition, making them weak and anaemic.
(b) Causing disturbances to the patients by mechanical injuries and obstruction, G. I. disorder and colic pains. (c) Causing systemic disorders like urticaria and eosinophilia.

Examination of stool for the detection of ova and of blood for eosinophilia, will clinch the diagnosis.

Plate XXXIII

DIAGRAMMATIC REPRESENTATION OF COMMON INTESTINAL PARASITES AND THE DRUGS EFFECTIVE AGAINST THEM

Mepacrine
Chloroquine
Filixmas

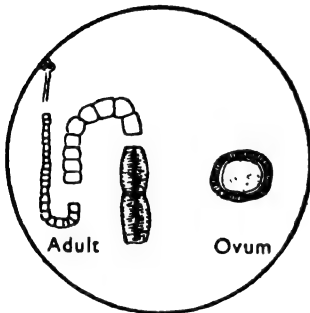


Fig. 90. TAPE WORM
(*Taenia solium*)

Bephenium hydroxynaphoate
(Alcopar)
Tetrachlorethylene

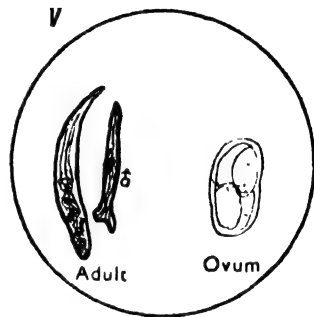
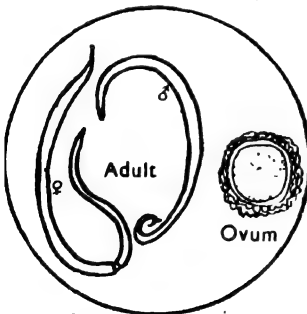


Fig. 91. HOOK WORM
(*Ancylostoma duodenale*)

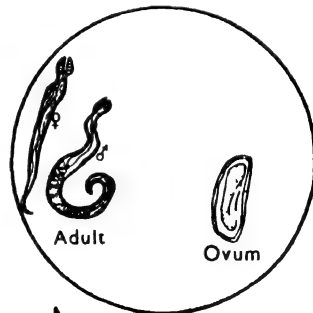
INTESTINAL HELMINTHS AND DRUGS ACTING ON THEM

Fig 92. ROUND WORM
(*Ascaris lumbricoides*)



Piperazine

Fig 93 THREAD WORM
(*Enterobius vermicularis*)



Piperazine
Gentian violet

The word '*anthelmintic*' refers to the action of drugs against intestinal worms. Only a few of them possess any true inhibitory and lethal effect on worms and are known as '*vermicide*'. Majority of them possess non-specific types of action, loosening their grip on the intestinal wall. They are then expelled by purgatives. These in reality, act as '*vermifuge*' by expulsion of worms. In a few cases both the actions may be combined.

Mode of Infection: This differs with different types of worms and also with the *infective units* of ova or larvae. The infective units of ovum of the ascaris, oxyuris and the whip worm and the infective units of larvae of taenia, trichinilla and guinea worms, enter the human body by the oral route through uncooked vegetables with faecal pollution or contaminated finger nails, as in the case of thread worm. The tissue worms usually enter the human body through the infected meat as in the case of *Trichinella spiralis* and the liver fluke and through infected water of step well in the case of the guinea worm.

Larvae of hook worm, schistosoma, strongloides and filaria enter into human body through the skin, the last by the bite of culex mosquito. These organisms then undergo different stages of evolution in the human system itself.

(a) Worms like taenia, thread worm and whip worm evolve to the adult forms in the intestine and the females start laying the eggs.

(b) Ascaris, hook worm and strongloid pass through a phase of larval development in the lungs and from these via bronchi, trachea, larynx and pharynx, they reach the oesophagus.

(c) *Trichinella spiralis* larvae pass through the intestinal mucosa and settle down in the skeletal muscles.

(d) The microfilaria evolve into the adult forms and block the lymphatics.

(e) The larvae of schistosoma which have a cycle in snails, evolve into adult worms in the portal circulation and reach the bladder and produce haematuria.

The helminths that harbour in the G. I. tract, produce obstruction symptoms in bowel as by round worm or in the appendix as seen in pin worm infestations. Hookworm, round-worm, trichuris and tape worms give rise to bowel disorders, sometimes acute diarrhoea or dysentery like symptoms. Severe microcytic and macrocytic type of anaemia is produced in hookworm and *D. latum* infestations, respectively. Fever and elephantiasis are present in filaria, cirrhosis of liver

in fluke, while fevers, urticaria and haematuria are observed in schistosomiasis.

Helminths like roundworm, hookworm and strongyloid, the larvae of which pass through the respiratory tract, produce respiratory symptoms as in asthma. They also produce a condition known as 'eosinophilic lung', which is characteristically seen in filariasis.

In trichinella and taenia infestation, earlier symptoms refer to the G. I. tract and later, symptoms of urticaria, fevers, muscular or nervous disorders, occur.

Method of Study: These are yet fairly crude and qualitative. The evaluation is carried out: (a) On the strips of worms in isolated organ baths. (b) After inoculation of suitable animals like dogs and rats and then by carrying out the faecal egg counts before and after the drugs therapy. (c) Biochemical enzymatic studies for determining the mechanism of action of drugs.

Mechanism of Action: It is yet very little known and that is why the progress in the discovery of anthelmintics has been so slow, in spite of magnitude and seriousness of the problem. The following are the tentative hypothesis:

(a) Stimulation, depression or paralysis in the grip of the worm by drugs, making their hold on the intestinal wall unsteady. These have been conceived but not fully substantiated, due to experimental difficulties.

(b) An attempt to explain drug actions through metabolic changes in the worms has not been fully successful as in the absence of the laboratory culture technique of worms which also varies from worm to worm, a biochemical approach to the problem has not worked.

(c) However, (i) inhibition of succinic dehydrogenase affecting the metabolism of roundworm and threadworm by piperazine and (ii) inhibition of phospho-fructokinase and glycolysis in schistosomes by antimonials, have been observed. This new approach with further advances, is likely to yield newer drugs of more specific nature, for the helminth in the future, judged from the discoveries of recent years.

An Ideal Anthelmintic: As most of the drugs are at present effective almost at the toxic level of doses, there are not many ideal anthelmintics as yet, the prerequisites for which should be: (a) Selective toxicity for worms and not for the host tissue. (b) Nonabsorption and non-irri-

tation of the intestine. (c) Simplicity and cheapness in the method of treatment. (d) No dislocation of work and sure efficacy.

MEPACRINE

An old antimalarial, which of late, has shown its value in tape worm infestation also. It is selectively concentrated in the scolex of the worm and not in the intestinal tissue of the host and by causing relaxation of the holding muscles, by the reversal of the electrochemical forces in the grip of the worm, it facilitates vermifuge action of the purgative.

It is given in doses of 0.2 gm/every 10 minutes/4 doses, followed by a saline purgative after 2 hrs.

The child dose is $\frac{1}{2}$ of it, suspended in milk. It is most effective in *T. solium* and *T. saginata* infections, with 70% cure rate and more so, with a second course after a week. The drug is remarkably atoxic, compared to filixmas.

Chloroquine and camoquinin: Doses of 250 mg./10 kg., with a maximum of 2 gm, is recommended in *H. nana*, *D. latum* and other dwarf worm infestations.

FILIX MAS

The rhizome of *male fern* used since the days of *Galen* and *Fliny*, the oleoresin, an ethereal extract containing *filicin*, a fluoroglycin, a dark green sticky substance, is used in the tape worm infestation, in the dosage form of extract filicis or oleoresin aspidium—1.5 gm., in gelatin capsules of 5 gm./half hrly/4 doses.

It is of limited value, because of its neuromuscular toxicity: hyperexcitability, xanthopsia, muscle cramps, C. V. depression and amblyopia. If absorbed in sufficient quantities, it produces G. I. irritation, nausea, vomiting and abdominal cramp.

The drug is contraindicated in alcoholics, during pregnancy, in ulcerative conditions of the G. I. tract and with castor oil purgative, which facilitates its absorption.

Dichlorphen: It is a new drug for the treatment of *taenidsis* and is given in a dose of 0.5 gm/7.3 kg. of body weight. It is less reliable than male fern and may cause abdominal pain, diarrhoea and jaundice.

Niclosamide: It is effective against tapeworm infestation and is given in a dose of 1 gm, followed by another dose of 1 gm, one hour later.

In the treatment of taeniasis with these drugs, preparation of pati-

ents by withholding food-fat for a day, use of soda bicarb and glucose, magsulph purgative and soapsud enema, may be necessary for effective vermifuge action.

Pelletierine: A mixture of alkaloids, obtained from the bark of pomegranate (*Punica granatum*). *Dose:* 0.25 gm. of the *tannate salt*. It is less effective and much less toxic and no elaborate preparation of the patient is necessary. In view of its uncertain effectivity, its use in taeniasis has been practically given up.

Oil of Chenopodium: a mixture of volatile oils, obtained from the Jerusalem oak of North America. It is moderately effective in ascariasis, hook worm and tape worms infestations, in doses of 1 ml/in divided doses/capsules of 3 *min* each, at an hourly interval. Due to its toxicity, it is not much used these days.

TETRACHLORETHYLENE ($\text{CCl}_2\text{-CCl}_2$)

A clear, colourless liquid of charactersitic odour. *Dose:* 1-3 ml. in gelatin capsules of 0.5-1 ml. It is very little absorbed from the G. I. tract, if fatty food and alcohol are withheld.

Toxicity: Much less, but of the type of CCl_4 (a) dizziness (b) vertigo, (c) headache, (d) nausea (e) drowsiness and (f) also some amount of hepatotoxicity. It is *contraindicated* in (a) G. I. inflammation, (b) Severe anaemia and debility, (c) Alcoholism and (d) Ascariasis.

Uses: A drug of choice for (a) hook worm infestation and also used in (b) trichuriasis, (c) oxyuriasis.

CARBONTETRACHLORIDE

A volatile liquid and a general protoplasmic poison which is absorbed from the G. I. tract and is intensely toxic for the liver, producing *acute hepatic failure*. It is because of this that in spite of its therapeutic efficacy, it is seldom used nowadays. *Dose:* 1.5-3 ml. in capsules.

THYMOL

A phenol obtained from *Thymus vulgaris* and is an old anthelmintic, used since 1879. It is completely absorbed from the G. I. tract in the presence of fat and may produce C. N. S. depression. *Dose:* 1 gm.,

2 or 3 doses, with lactose or NaHCO_3 , followed by a saline purgative. It is no more used as an anthelmintic since the introduction of tetrachlorethylene, but it is still used as an antiseptic for the preservation of urine and tissues.

HEXYLRESORCINOL

It was introduced as an effective agent against ascariasis, tape worm and hook worm infections by Lamson in 1930. It is partly absorbed from the G. I. tract and is excreted in urine. It is an irritant for the skin, producing numbness. Its overall toxicity is low, permitting the repetition of treatment. *Dose:* 1 gm/os/divided doses/in gelatin coated pills of 0.1 and 0.2 gm. For children below 10 years, 0.1 gm/year of age.

The drug is taken in empty stomach in the morning without chewing, Food is withheld for 5 hours and an after saline purgative is given. No preparation of the patient is necessary. It is the drug of choice for mixed infection with ascaris and hook worm. It is also a urinary antiseptic.

SANTONIN

The flowering tops of *Artemisia maritima* yields santonin which is an effective vermifuge for ascariasis.

A small amount is absorbed and oxidised in the body, excreted in faeces and urine, as an oxysantonin, imparting yellow colouration to the skin, xanthopaia, G. I. upset, skin eruptions and even convulsions, in large doses. *Dose:* Adults 0.06-0.2 gm./in divided doses *Children:* 10 mg./year of age. The drug is absorbed more readily in the absence of food, oils or fats. A saline purgative is given and the drug is not repeated within a week. Bile salts increase its activity and calomel and MgSO_4 purgatives are usually recommended

PIPERAZINE (ANTEPAR)

It is the drug of choice in *oxyuris* and ascaris infestations. *Piperazine citrate*, in syrupy form: 50 mg/kg. upto 2 gm. daily, is given for 5-7 days. Even two days therapy has been found to be effective in 95% of cases of *ascariasis* and 2 weeks treatment in oxyriasis. It causes nausea, vomiting, headache, abdominal cramps, urticaria and also mild diarrhoea. It is much less toxic than gentian violet and is not unacceptable to the children.

ALCOPAR

Bephenium hydroxynaphthoate, a broad spectrum anthelmintic, acting chiefly on *hook worm*, but also on *round* and *thread worms*. *Dose*: 5 gm., single dose. It is a popular drug these days.

Phenothiazine: Though widely used in veterinary medicine for the treatment of helminthiasis, it is not used in human therapeutics, because of severe haemolytic anaemia.

GENTION VIOLET

It is a dark green, water soluble powder and a powerful antiseptic for gram positive organisms. It acts specifically in *thread worm* and also in *strongyloid* and *trichuria* infections. It is a fairly safe drug and has also the advantages of easy administration and cheapness. It causes mild nausea, vomiting, diarrhoea and colic pain, which cease on stopping the administration of the drug for 1 or 2 days. It is *contraindicated* in patients with organic lesions of the G. I. tract and concomittant ascaris infection, which is to be treated first. The *adult dose* is 30 mg. tablet, thrice a day and for *children*, 10 mg. tabs, thrice a day, for 10 days.

DIPHENAN

A p-benzyl phenyl carbamate, which destroys oxyuris. It is used in *doses* of 0.5-1 gm t.d.s., in the form of tablets of 0.5 gm after meals, for one week, followed by castor oil purgative. For children below 2 years: $\frac{1}{4}$ tab., below 10 years $\frac{1}{2}$ tab., over 10 years—1 tab. and for adults —2 tab. t.d.s.

CYANINE DYES

A recent addition to the armamentarium of anthelmintics with marked therapeutic index in cotton rat *filariasis*. It has inhibitory action on the oxygen uptake of the parasites, about 1000 times more than for the host cells. It also increases the aerobic glycolysis of the parasite.

Pyriwinium Pamoate: A cyanine dye which is more effective than gentian violet in *oxyuriasis*. A flavoured suspension containing 10 mg./ml. *Dose*: 5 ml. or 1 tab./10 kg. is used. It has very little toxicity but 96-100% cure rate, in a single dose therapy.

Dithiazanine Iodide: Another cyanine compound which is effective in *ascariasis* and *oxyuriasis*, as well in *trichuriasis*, *strongyloidosis* and *hook worm* infections.

A combined treatment with tetrachlorethylene produces the best result in the last condition. Due to its broad spectrum of activity, it is considered to be a good drug for *mixed infections*. *Dose:* 45 mg./kg., with a maximum of 600 mg./day, for 5-10 days, in the form of tablet or cherry flavoured suspension of 20 mg/ml.

MANAGEMENT OF HELMINTHIASIS

This is complicated in view of the inadequate knowledge of the sensitivity of different worms in different phases of their evolution without which specific therapy cannot be discovered for effecting any radical cure. Further, till unsatisfactory public health measures continue in a country, the chance of reinfection and superinfection cannot be remedied.

Management of intestinal helminthiasis comprises the therapeutic measures as detailed hereunder:

Tape Worm: (a) At present the drug of choice for taeniasis, particularly the *saginata* group, is *mepacrine*. (b) Preparation of patients, preparatory saline cathartic in the evening and *mepacrin* 0.2 gm., 4 doses at short intervals, followed by a saline purgative after a few hours and also enema, if necessary. (c) Very occasionally, filixmas and pelletierine are indicated in *Taenia solium* and chloroquine and camoquine for dwarf worms.

Round Worm: (a) *Piperazine citrate (antepar)*: 2-3 gm., in the form of tablet or elixir, is the drug of choice. Sometimes one dose therapy without purgative may be adequate. Its advantages are less toxicity, simple therapy and 100% result in unmixed infection. (b) *Hetrazan*: 6 mg/kg. and hexyl resorcinol for mixed infection. Santonin and oil of chenopodium are much less popular these days. No preparation of the patient is required in these cases.

Hook Worm: Its management comprises two important issues, (a) Treatment of associated anaemia by appropriate diet, iron and small transfusion therapy and (b) Associated ascariasis infestation, which has to be treated first before going to the second part of the therapy.

The drug of choice has so far been *tetrachlorethylene*: 1—3 ml. along with *dithiazine iodide*, for 5-10 days, not exceeding 600 mg. per day. Nowadays, *alcoapar* is preferred.

The use of carbon tetrachloride, thymol and β -naphthol has been relegated to the background. A single dose therapy of 5 gm. of *alcoapar* often suffices.

Thread Worm: (a) *Piperazine citrate* (*antepar*) is the drug of choice. Gentian violet is also effective to the extent of 90% but is contraindicated in mixed infection with *ascaris*. (b) *Piperazine* is much less toxic, more efficacious and also available in syrupy form: 250 mg/day, two courses of 7 days each, often suffice.

Strongyloidosis: *Gentian violet*: 65 mg. t.d.s. and in doses of 10 mg./day/year, for children and also *dithiazine iodide* are fairly efficacious.

Trichuriasis: (a) No specific drug is available but *cyanine dyes*, in the form of *dithiazine*, oil of *chemopodium*, *tetrachlorethylene*, *hexylresorcinol*, orally or as retention enemata, may be tried.

In spite of all these, the management of the worm infestation, its reduction in incidence and deworming of the population, are not very easy. For even partial success, need for early diagnosis, by frequent stool examinations, adequate specific therapy for making the patient free from infection, elimination of risk of reinfection by the treatment of all the family members and school going children and above all, periodical check up of the treated and untreated cases by stool examination, to ensure continued freedom from infection, are essential.

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SECTION
X
CHEMO AND ANTIBIOTIC THERAPY
CHAPTER
42
PHARMACOLOGY OF ANTI-INFECTIVE DRUGS

GENERAL CONSIDERATIONS; HISTORICAL DEVELOPMENT, SCOPE OF
ACTION AND MODE OF STUDY. PROBLEMS OF TOXICITY AND RESIS-
TANCE FORMATION.

[Chemotherapy or treatment of infectious diseases by synthetic or other chemical drugs is a new approach to the pharmacotherapeutics of specific nature. The predilective staining properties of different organisms made Ehrlich think about the possibility of having drugs with selective parasitotropic but not organotropic action, with high therapeutic indices. This led to the discovery of *salvarsan*, which was soon followed by the discovery of other antisyphilitics, antimalarials, amoebicides and drugs for other parasitic diseases. After 1935, the *sulphonamides*, antibiotics and antitubercular drugs were discovered, giving a powerful array of specific drugs, both for *parasitic*, as well as, *baeterial* diseases, which have completely revolutionised the prognosis of most of the erstwhile fatal diseases.

The *specific* action of chemotherapeutic and antibiotic drugs envisages biochemical planes of activity, disturbing the utilization of metabolites, essential aminoacids, vitamins, purines and pyrimidines, by the complicated enzyme systems of pathogenic organisms. Being potent drugs, they may however, sometimes act like 'double-edged weapons' producing far-reaching toxic manifestations, in the host and also resistance formation in the micro-organisms.

The chemotherapeutic drugs available at present, may be classified as (a) antiparasitic, (b) antibacterial, (c) antirickettsial, (d) antiviral, (e) antifungal and (h) antimalignancy ones and are screened by *in vitro* and *in vivo* tests, in culture media or in experiment animals, for assessment of anti-infective properties and toxicity hazards.

The chapter thus, is a fastly developing, challenging one and the present concept of chemotherapeutic and antibiotic drugs as separate entities, will cease when the latter, which are at present, mostly of fungal origin, are successfully synthesised. All these specific drugs will then be able to have the common nomenclature of *chemotherapeutic agents*.]

Most of the drugs used before the discovery of specific therapies for infectious diseases, were of palliative nature. In parasitic and bacterial

Plate XXXIV

PIONEERS OF ANTI-INFECTIVE THERAPY

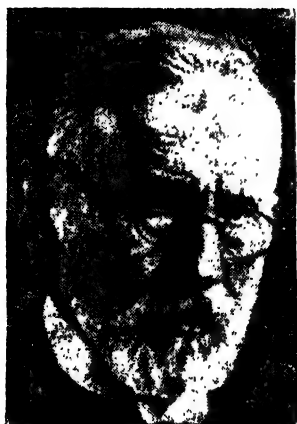


FIG. 94 *Paul Ehrlich*
(Father of chemotherapy)



FIG. 95 *Alexander Fleming*
(Discoverer of penicillin)



FIG. 96 *G. Domagk*
(Discoverer of prontosil)

infections, curative agents should be able to inhibit, destroy or eradicate the causative organisms without causing any damage to the host tissues. The term *Chemotherapy*, literally means 'treatment of diseases by chemical drugs'. More recently, it has been defined as a specific therapy of systemic infections, by chemical synthetic drugs, including prophylaxis, as well as, drug therapy of malignant diseases, provided that the action is of a specific nature. Most of the drugs employed for this purpose, produce their actions on the biochemical, enzymatic and metabolic pathways of infective organisms or other tissues; and consequently, their actions are often indirect, more specific and occurring at comparatively lower concentrations, thus sparing the host cells from damages, to the extent possible. At least, these had been the original concepts underlying the enunciation of chemotherapeutic agents as remedial measures.

Historical Development: Though the use of mercury in syphilis and quinine in malaria had been existing from the 15th and 17th centuries respectively, real chemotherapy started with the magnificent work of Paul Ehrlich (Plate XXXIV; Fig. 94) towards the end of the last century, when he pleaded for a single drug, a dose of which, would sterilise all infections. This he named as *therapia magna sterilans*. This effort, of course, could not materialise, but it resulted in the discovery of 'antisyphilitic organic arsenicals'. The word chemotherapy was introduced by him in the year 1891, along with his famous *postulates* of defining specificity of action to (a) the analogy of individual lock and key, (b) parasitotropic as against organotropic actions and also the (c) concepts of therapeutic index to be more than 3, as 'safety margin', for the host. With the passage of time and the wealth of accumulated experiences, though it is now known how difficult it is for any drug to fulfil all these prerequisites, that does not minimise the importance of the postulates of the 'Founder of Chemotherapy' and preclude their realisation with further advances in drug synthesis, at a future date.

This new concept of great magnitude set thousands of workers all over the world to work in this new field of research and within a short span of 60 years, 'drug synthesis' has been firmly established, putting up a real challenge to other forms of drug therapy by discovering *specific drugs*, not only in infective conditions but also in so many other fields of disease processes.

The study of 'structure-action relationship' of natural and synthetic compounds and the appreciation of the need of team work in research, in connected fields of sciences, have led to further developments of

chemotherapeutic agents. Attachment of the side chain of methylene blue, a known weakly antiplasmodial dye stuff, to various heterocyclic systems, has produced important antimalarials of *pamaquin* and *quinacrine*. Other research efforts in U. S. A. and Great Britain during 1940-46, have given chloroquin, camoquin and paludrine, as suppressive and curative agents in malaria.

Although synthetic chemotherapeutic agents were made available during the first two decades of this century for various types of parasitic diseases, bacterial infections could not be treated with chemical drugs till 1930. Consequent to the failure of Koch to cure septicaemia with all known antiseptics, it was believed that chemotherapy was meant for parasitic diseases only. The most significant advance in this field was made in 1935, when Domagk (Plate XXXIV: Fig. 96) announced that the *red dye prontosil* could protect acute systemic bacterial infections from streptococci, to the extent of 1000 LD in animals. Work of Nitti, Bovet and Trefuel of the Pasteur Institute of Paris, established that the active moiety of this dye stuff was sulphanilamide, which led to the synthesis of a wide range of sulpha drugs, suitable for the treatment of most of the common infectious diseases.

The observations by Woods and Fildes in 1940, that the bacteriostatic action of sulpha drugs was antagonised competitively by para amino benzoic acid, led to the hypothesis of 'metabolite antagonism', which has been used successfully in the chemical planning of newer drugs. Antitubercular drugs, isonex and PAS, and antileukaemic agents like aminopterin, are the outcomes of this concept.

Sir Alexander Fleming (Plate XXXIV: Fig. 95), as early as 1929, starting his *antibiotic research*, produced a nontoxic bactericidal penicillin solution from the mould *penicillium notatum*. Before the rising tide of sulphonamides, this wonderful discovery remained without much notice, till Florey and Chain, in 1941, purified penicillin, the first and the most important chemical antibiotic. It was soon followed by the discovery of streptomycin (Waksman 1944), chlortetracycline (Duggar 1946), chloramphenicol, oxytetracycline, erythromycin and several others. Complex chemical structures of several antibiotics were elucidated and a few even synthesised. They were found efficacious for a wide range of bacterial, spirochaetal, protozoal, viral and fungal infections. More recently, some of these have been found useful even in the therapy of neoplasms and leukaemias.

Definition: A question has often arisen as to whether the chemotherapeutic and antibiotic drugs, both so efficacious for the treatment of infective conditions, are synonymous. The word *chemotherapy* refers

to chemical synthetic drugs, while antibiotics are obtained from the living organisms, mostly fungi and are effective against pathogenic organisms. Both therefore have similar actions while differing in their sources. However, several of the antibiotics have been chemically identified now and even partially or completely synthesised. When it will be possible to reproduce them completely by synthesis, they will also become chemotherapeutic drugs, in the strictest sense of the term.

Whatever may it be, with the advent of these highly potent chemotherapeutic and antibiotic agents, a profound change has been introduced into the medical practice and one can reasonably forestall that the *specific therapy* of synthetic nature, will one day, constitute the major part of drug therapy, in not a very remote future.

Chemotherapeutic Index: Ehrlich believed that his chemotherapeutic agents possessed maximal affinity for host tissues. This meant that they had maximum parasitotropic and minimum organitropic properties, in other words, a favourable '*chemotherapeutic index*', which is defined as the ratio of:

$$\frac{\text{Maximum tolerated dose.}}{\text{Minimum curative dose.}}$$

The greater the index, the greater is the therapeutic value of the drug. Sometimes more useful indices, enhancing the *safety margin*, as represented below, are used.

$$\text{Chemotherapeutic Index} = \frac{\text{L.D.—0.1}}{\text{C.D.—99.9}}$$

where LD 0.1, is the dose which kills only 0.1 % of the animals and C.D. 99.9 is the dose which cures all the animals excepting 0.1 %. These indices are used for indicating the value of drugs.

Specific Action: With the development of knowledge regarding the causation of different infections and the progress of synthetic chemistry, newer remedies are being introduced, which approach more towards specific actions. A specific drug is considered to be which acts in a condition, at a comparatively low concentration, mostly through the complicated enzyme systems in the infective organisms or on effector cells of the body.

The *specific action* of chemotherapeutic drugs has been explained through a selective interference with certain phases of microbial metabolism.

(a) A chemotherapeutic agent may inhibit the synthesis of a relatively simple metabolite which is essential for the pathogenic organisms. In this way, a number of subsequent metabolic reactions, based on the availability of the metabolite, is blocked and the growth and multiplication of the organism checked.

(b) A drug may be structurally similar to the metabolite and capable of interfering not only with the utilisation but also in the process of conversion of more complex materials needed for the microbial cell.

As vitamins, amino acids, essential fatty acids, purines and pyrimidines play significant roles in the metabolism of organisms, knowledge of their anabolic reactions is of great importance for the development of chemotherapeutic drugs. The synthetic rather than the catabolic activity of the organisms differs significantly from the capacity of the mammalian host cells making the selective chemical attack upon the parasite, possible.

Many drugs act as specifics within the body of the host, while possessing little effect outside it. In such cases, so many other factors like, biotransformation, defence mechanism of the body, the intricate chemical work carried out by the system, may come into play. In fact, we still know so little about the complicated working of the biological systems, to be able to understand the precise nature and mechanism of drug action under the paradox of innumerable variables and chain reactions.

Evaluation: The screening of chemotherapeutic agents is carried out by (a) *in vitro* and (b) *in vivo* tests.

1. *In vitro tests:* The organisms against which an activity is to be tested, are cultured in the test tubes, containing a liquid medium or on agar cup plates and the inhibitory effect of the drug is seen by adding it to the culture. Modifications of this technique include *streak test*, *cup plate assay* procedures, which are commonly employed in the quantitative measurement of antibiotic activity. *Broth dilution* procedures are also useful.

If a test organism cannot be cultured, without the presence of blood or tissue cells of a host, then the *in vitro* method may have to be combined with an *in vivo* test, to some degree. More clear-cut *in vitro-in vivo tests*, involve infections of the *chorioallantoic membrane* of the *chick embryo*.

Inhibition of multiplication of the microbial population is called *stasis* (i.e. *bacteriostatic*), while a decrease of the viability of a culture indicates the *cidal* (i.e. *bacteriocidal*) property of a drug.

In some cases, the results of *in vitro* studies are not substantiated by *in vivo* studies. This may be due to the biotransformation of drugs, stated earlier, cell permeability, protein binding, lipoid solubility and a number of barriers, present in the host tissues.

2. *In vivo tests*: The chemotherapeutic activity of a compound is usually measured in laboratory animals, infected with a test organism. In some cases, bigger animals may have to be used as hosts. The animals are infected parenterally with an inoculum of the pathogenic organism to produce the infection. This may be treated with a test drug. If the prophylactic properties of a drug are to be measured, the animal is first treated with the drug and infected after a given time-interval. An optimal blood concentration is an essential prerequisite for the evaluation of chemotherapeutic agents.

With many virulent strains, the test animals die within 48 hours, after infection and treatment for 3 days is therefore sufficient to determine the effectiveness of a drug. Compounds of promising nature are also subjected to pharmacodynamic studies, including *acute* and *chronic toxicity* tests. Finally, the drug is passed on for *clinical trials* for assessment of efficacy and side-effects, in human patients. In all these complicated manners, a new drug has to be carefully evaluated for a number of years prior to its use in general therapeutics.

Hazards: Like other potent drugs, chemotherapeutic agents act like 'double-edged weapons' producing *magic effects* on judicious uses in appropriate cases and *toxic effects* in high doses with the possibility of reacting on the enzyme systems. Misuse of chemo and antibiotic drugs may lead to:

(a) *Toxic manifestations* of vital nature. (b) Sensitization reactions affecting the skin and (c) Resistance formation.

All these are annoying problems and are of intrinsic nature in specific drugs acting on the biochemical and cellular levels. That is why search for newer compounds are continuously going on eliminating the limitations of the former and in turn, adding newer ones in future.

Classification: These hurdles have been standing in the way of assigning any fixed fulcrum on the efficacy of these drugs in respect of certain organisms which due to their exclusive nature, also differ in their selectivity in response to a drug, while belonging to the same broad family. Classification of chemotherapeutic and antibiotic drugs, organism-wise, in any general manner, is not therefore easy. That the

micro-organisms possess special affinity even in staining properties had been known to 'Ehrlich', which in fact, gave him a clue to search for drugs with selective action. In this respect, not only the *bacteria*-gram positive and negative, cocci and bacilli, but *spirochaetes*, *protozoa*, *rickettsiae* and *viruses*, all differ in their properties, from one family to another, and even in the same family.

Microbiological Considerations: The microorganisms which are amenable to chemo and antibiotic therapies, belong to very different groups, each having its own characteristic (Plates XXXVII Fig 99-101 and XXXVIII Fig. 102-105). The *cocci* are spherical gram positive and negative organisms arranging either in chains, clusters or in pairs, as in the cases of strepto, staphylo, pneumo, meningo and gono cocci. The *bacilli* are straight or slightly curved, some motile others non-motile, in pairs or in chains—*B. salmonella*, *shigella*, *anthrax* and *B. tuberculosis*, all gram negative organism with the exception of *B. anthrax* and *B. tuberculosis*, which are gram positive. Further, tubercle bacillus has also its characteristic staining properties. The *vibrios* are tiny, comma shaped, highly motile, gram negative organisms such as, *V. cholerae*, producing cholera. The *spirochaetes* are thin, flexible, gram negative organisms with spirally twisted filaments along the axis, visible better by 'dark-ground illumination'. They are motile, having no flagellum—*trepanoma pallidum*, *pertenuis* and *vincenti*, causing diseases like syphilis, yaws and vincent's angina. The *actinomycetes* are higher types of gram positive bacteria with branching e.g. *A. bovis*. The *viruses* are minute ultra-filterable and ultramicroscopic organisms, much smaller than the bacteria. They multiply in the living cells and produce 'inclusion bodies'. They cause diseases like rabies, small pox, pneumonia, encephalities, lymphogranuloma, trachoma, chicken pox etc. The *rickettsiae* are rod-shaped organisms, smaller than bacteria but larger than viruses, as in the case of *R. prowazekii*. This group of organisms produces typhus and Q. fever. The *protozoa* are mobile, unicellular, nucleated and have a sexual phase of reproduction e.g. *plasmodium*, *amoeba*, *leishmania*, *giardia* and *trypanosomes*. The *fungi* are low forms of vegetable life, capable of producing superficial and systemic infections of a tenacious nature, such as *moniliasis*, *actinomycosis*, *histoplasmosis*, *blastomycosis*, *coccidioidomycosis*, *aspergillosis* and ringworm (Plate XXXIX Fig 106).

The above is an outline of the different genera of infective organisms, for some of the varieties of which and not for all, the chemotherapeutic and antibiotic drugs find their uses. Nevertheless, we do

not yet have appropriate therapy for a number of conditions like rabies, smallpox and Q. fever.

With increasing scope of use of newer and newer chemo and antibiotic agents in microbial and other diseases, though it is not easy to categorise these drugs either disease or organism-wise at present, from a broad point of view, their conventionally acceptable *groupings*, may be taken as:

- | | |
|---------------------------|--------------------|
| (a) Antiparasitic | (b) Antibacterial |
| (c) Antiviral | (d) Antifungal and |
| (e) Antimalignancy Agents | |

In the subsequent Chapters, they will be dealt with under the *broad headings* of:

- (a) Antisymphilitics, (b) Antiprotozoal and other antiparasitic agents.
- (c) Sulphonamides (d) Antibiotics,
- (e) Chemotherapy of T. B., Leprosy and Urinary tract infections,
- (f) Antineoplastic and immunosuppressive agents.

The above preclude many other areas of chemo-antibiotic therapies, which will be discussed in the body of the text, at their proper places.

CHAPTER

43

CHEMOTHERAPY OF SYPHILIS

MAJOR AND MINOR DRUGS. THEIR RELATIVE SPECIFICITY, TOXICITY AND THERAPEUTIC STATUS IN SYMPTOMATIC AND BIOLOGICAL CURE OF SYPHILIS

[Before the discovery of chemotherapeutic drugs, syphilis through ages, had been one of the most crippling diseases of the world, with high incidences of acquired and congenital syphilis and complications and sequelae.

Though arsenic, bismuth and to a smaller extent, mercury and potassium iodide, have been the drugs in use, in modern therapy, *penicillin*, with its special preparations, is the most important single antisyphilitic-antibiotic and along with some uses of bismuth, for consolidation, meets with the dream of 'therapia magna-sterilans' of Paul Ehrlich.

Amongst the trivalent arsenic preparations, mapharsen, chlorarsen and oxarsen have been in use in syphilis, while the pentavalent tryptersamide, stovarsol and carbarson for other infections. Bismuth preparations—watery and oily solutions and suspensions, are effective antisyphilitics with some roles in the 'consolidation of effect. Both these drugs, however, are toxic and therefore little used in the treatments of today.

Penicillin alone, is able to deal with most of the stages of acquired, as well as, congenital syphilis and other antibiotics—erythromycine, terramycine, chloromycetine and streptomycin, only form the second line of drugs, with very restricted fields of use.

In primary, secondary and latent syphilis, aqueous penicillin, PAM or benzathene penicillin, in 2-4.8 mega units, are given, while still higher doses may be prescribed in late syphilis, sometimes.]

These drugs which constitute a major landmark in the therapy of syphilis, reducing it from its erstwhile alarming prognosis of an incurable and maliciously contaminating disease, to the present position of a dangerously carefree attitude of mind, comprise *two* distinct groups—*major* and *minor*, which are again undergoing frequent changes, because of the shifting of emphasis, due to newer drugs. Thus the order of arsenic, bismuth and mercury, has now changed to penicillin and bismuth, arsenic being relegated to a very secondary position, compared to penicillin.

CLASSIFICATION

Major	Penicillin and its special dosage-forms. Bismuth and its injectable preparations. Organic arsenicals in tri and penta-valent forms.
Minor	Other antibiotics—erythromycin, tetracyclines and streptomycin used sometimes only in penicillin resistant and hypersensitivity reaction cases. Mercury and its antisyphilitic preparations. Potassium iodide in tertiary syphilis and its complications.

Of these, inorganic arsenic, bismuth and mercury, having already been detailed in Chapter 34, of Metals, their organic and other preparations pertaining to antisyphilitic uses mostly, will be dealt with in this chapter.

ORGANIC ARSENICALS

The preparations of organic arsenicals are divided into *two* series of compounds:

1. *Aliphatic Compounds*: Iron and sodium cocodylate—15 mg. OS/SC/IM, used in chlorosis and chorea, but not as an antisyphilitic.

2. *Aromatic Organic Compounds*: (i) Trivalent and (ii) Pentavalent forms, used as antisyphilitic, trypanocidal and amoebicidal agents.

Preparations: Numerous, both of trivalent and pentavalent forms.

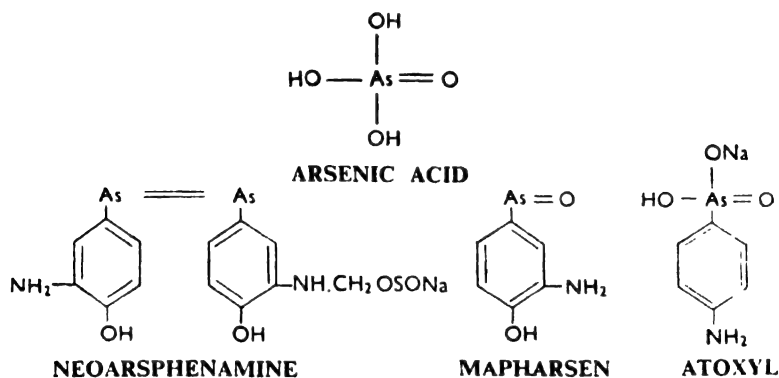
Trivalent: *Arsphenamine* 606, 'Salvarsan—the salvation of the syphilitics', the original compound of Ehrlich, most potent but unstable and toxic and has long been withdrawn. Similarly *sulpharsen* and *Bismarsen* though having the advantages of S. C. and I. M. inj. respectively, are no more used. *Neotrsphenamine* (N. A. B. 0.15-0.9 gm. 10-12 biweekly I. V. injections, had been a dependable preparation and much used for trypanosoma and spirochaetal infections, *Mapharsen*, *Chlorarsen*, *Oxarsen*—30-60 mg. 10 I. V. inj. which had replaced NAB in the pre-penicillin era, have also in turn, been replaced by penicillin.

Pentavalent: *Atoxyl*: 125 mg. S. C., the original compound of Ehrlich for trypanosomiasis, is seldom used for reasons of optic and other toxicities. *Tryparsamide*: 250 mg. 12 I. V. injections, is used for trypanosomiasis and *Stovarsol* and *Carbarson*: 250 mg/OS. t.d.s. for 10 days, in amoebiasis.

These preparations have varying amounts of arsenic contents: 15 to 30%. The trivalent preparations were better suited for early syphilis

and spirochaetal infections whereas the pentavalent compounds, used for trypanosoma and amoebic infections, as well as neurosyphilis, have to be converted to the trivalent form in the body for their antisyphilitic action and are toxic for the optic nerve.

Chemistry: The *trivalent* compounds are derived from arsenic trioxide or *arsenious acid*: As_2O_3 and the *pentavalent* compounds are derived from *arsenic acid*.



Illustr. XXII. Chemical structure of Neoarsphenamine, Mapharsen and Atoxyl

They are supplied in powder form, in nitrogen filled ampoules. The solutions, even when prepared with special precautions avoiding oxidation, gain 50% toxicity in half an hour. The solution is colloidal in nature and is liable to produce *nitritoid crisis*, which is a flocculation phenomenon.

Metabolism: (a) After injection, arsenic has a short sojourn in blood. The maximum excretion takes place within the first two days but a trace is detectable even up to the third month. The excretion occurs both in *organic* and *inorganic* forms; about 18 mg/day in stool and 2 mg in urine, in pentavalent form.

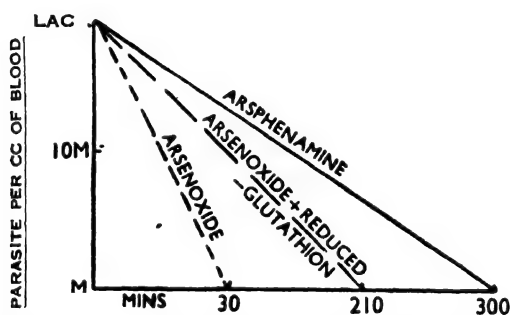
(b) Pentavalent arsenicals are more loosely fixed in the tissues and more quickly excreted. *Silver arsphenamine* diffuses into the C. S. F. more easily than the other preparations of arsenic.

Methods of Evaluation: (a) Toxicity test in mice and rats. (b) Therapeutic efficiency test in (i) infected guineapigs and rats with *T. equiperdum* and (ii) syphilitic orchitis in rabbits (c) Clinical evaluation, (i) Sterilisation of surface organisms-arsphenamine and mapharsen in 24 hours, novarsen 2-3 days; bismarsen 6 days and tryparsamide never.

(ii) healing of skin and mucous membrane lesions within 2-3 weeks by arspenamine→mapharside→Ag. arspenamine→bismarsen, in this order. Novar is weaker in this respect. (iii) Negative W. R., at the end of the first course, arspensmine in 75% of cases, also mapharsen, Ag. arspen and bismarsen. Novar is slightly weaker.

From the above, the relative position of efficacy of trivalent arseni-arsenicals is known. Mapharsen and arspenamine appear to be the best but as arspenamine is very toxic and mapharsen even less toxic than novarseon, the latter used to be preferred.

Mode of Action: In forms introduced, arsenicals are not treponemocidal *in vivo*, nor *invitro*. Hence, the roles of the tissue factors are important. According to Voegtlin, they are activated by partial oxidation to arsenoxide in the body. *Treponema pallidum* possesses SH group, with which arsenoxide combines and disturbs the respiratory metabolism of the parasite. Reduced glutathione is a physiological antidote of arsenoxide and slows down its action.



Illustr. XXIII. Comparative effect of arspenamine and arsenoxide and the role of reduced glutathione on arsenoxide.

Toxicology: 'Numerous'—both *local* and *systemic* and the latter again (a) immediate, (b) early and (c) delayed.

Locally: Arm pain, induration and thrombophlebitis, sulphar and bismarsen being the mildest.

Systemically: (a) *Nitritoid crisis:* an angioneurotic complex—with burning, anxiety, flushing, vomiting, perspiration, precordial distress and oedema. Frequency 1 in 1000 but not dangerous. The line of treatment comprises immediate stoppage of injection, adm inistration of adrenaline, changing novar to mapharside and keeping patient lying, for sometime after each injection.

(b) *Early Jarish-Herxheimer reaction:* From the massive destruction

of *T. pallidum* and liberation of endotoxin. Local lesions are excaggrated and arsephenamine is the worst, in this respect.

(c) *Nephritis: with albuminuria and casts:* Sulpharsephenamine and arsephenamine are the worst.

(d) *Exfoliative dermatitis:* Sulpharsphenamine being the worst. *Treatment:* with sodium thiosulphate: 1 gm./10 ml. I. V. and now B.A.L.

(e) *Hepatitis:* With jaundice, haematemesis and liver atrophy. Arsphenamine and neoarsphenamine are the worst. It is necessary to ensure that it is not due to syphilis, in which case, further continuation of treatment would improve the condition.

(f) *Haemorrhagic purpura*, polyneuritis, agranulocytosis and aplastic anaemia.

Uses: Besides syphilis, other uses refer to: (a) Spirochaetal and spirilla infections e.g. Vincent's angina, eosinophilic lungs, yaws and relapsing fever. (b) Pentavalent arsenicals are used in amoebiasis, giardiasis and trichomona infections.

BISMUTH

An important antisyphilitic, next in order to penicillin with special efficacy for consolidating the effects of other antisyphilitic drugs, besides its own action.

In addition to its oral use as G. I. protective, it has a number of complicated preparations, for parenteral use in syphilis.

ANTISYPHILITIC PREPARATIONS

Watery solution	Bismosol, thiobismol	Oily suspensions	Inj. Bi salicylatis, Oleo bismuthi
Watery suspension	Inj. bismuthi Inj. Bi oxychloride	Propylene-glycolsoluble	Iodo bismitol with saligenin: Sobisminol
Oily solution	Bismocymol and Quinby	Miscellaneous	Bismarsen, Bistoval Sobisminol mass or capsules.

The usual dose of these preparations varies from 1-2 c.c. I. M. once/twice a week, with a course of 12 injections. The aqueous preparations are best suited for rapid action of sterilisation when penicillin is contraindicated, while the oily preparations have a prolonged action and are meant for the 'consolidation therapy'.

Actions: The Levaditi School of workers (1922-1934), established the antisymphilitic status of bismuth from the following observations in rabbit syphilitic orchitis and also by clinical trials: Bismuth used *prophylactically* by deep I. M. injection, prevented syphilitic orchitis and given *after inoculation*, effectively suppressed the orchitic lesions, which flared up again after excision of 'bismuth depot' in the muscle. Bismuth was found to be converted to a tissue-soluble active form, *bismoxyl* and found to be effective in a concentration 2-8 Mg/gm. of tissue.

They were found to be absorbed in the following order: water soluble—watery suspension—oily solution—oily suspension. Bismuth was found to be distributed all over the body but the kidney and the liver retained it tenaciously. Excretion was mainly through the urine and only 10% through the gut.

Toxic Effects: (a) *Local* and (b) *Systemic*.

Pain, sterile abscess, sclerosing myositis, blue pigmentation of the gum, stomatitis and also jaundice, asthenia and hepatitis. In toxicity, arsenic is worst for the liver, mercury for the kidney, bismuth intermediate between the two and penicillin the least.

Clinical Status: Though much inferior to penicillin and arsenic, in the treatment of attack, it is complimentary to both and still used sometimes with the former, for the consolidation of effect and for the reduction of incidences of neuro-recurrence. It is also useful in cases of (i) Penicillin intolerance, (ii) Irreducible W.R. and (iii) Late syphilis.

ANTIBIOTICS

These are the latest additions in the therapy of syphilis, which have eclipsed practically all the hitherto known and used drugs.

Major Drug:
Penicillin

Others: Erythromycin
Chloromycetin
Streptomycin.

Though all these drugs will be dealt in detail in the Chapter of Antibiotics, it may be said, at this stage, that Penicillin is considered to be the most important single antisymphilitic antibiotic and all the other drugs are to be considered in penicillin intolerant or resistant cases, only.

PENICILLIN

From the voluminous data already accumulated, there does not seem to be any doubt that it is the most potent, selective and highly specific in its action. In a sense, it meets with the postulates of Ehrlich. Nevertheless, in view of the chronic insidious and treacherous nature of the disease, its apparent remissions with risk of serological recurrence, some more years should elapse, for the final assessment of its efficacy, in a long range manner.

- Status:** 1. (a) 50% of the organisms are immobilised in 16 hours at a concentration of 0.0025 units/ml and complete annihilation is effected in 1-2 weeks at a concentration of 0.1 unit/ml.
- (b) Development of pleomorphism and inhibition of multiplication are promptly observed after the administration of the drug.
2. It possesses curative, preventive, abortifying and prophylactic actions in all stages of syphilis—early, prenatal, during incubation and before exposure to contamination.
3. It is effective in all forms—latent, early, late, maternal and congenital syphilis, the exception being in C. V. and neuro-syphilis only, owing to advanced degenerative changes in the patient, as well as, difficulty in the diffusion of the drug in the C.S.F.
4. *Special advantages:* (a) Prompt action, (b) relative non-toxicity and inexpensiveness, (c) rare occurrence of resistance.

It is definitely superior to arsenic, though acting synergistically with mapharside.

Toxicity: It is of milder type and in a small per cent of cases only. (a) Allergic disorders. (b) Herxheimer reaction, but not of much serious consequence and less frequent than with arsenicals.

Other Antibiotics: Although penicillin is the drug of choice for all forms of syphilis, there are rare occasions when the patient may not tolerate it due to development of reaction. In such cases, alternative antibiotics, from out of, tetracyclines, erythromycin, chloromycetin groups, have to be considered for use. Among all these, only *tetracycline* and *erythromycin* are of real importance, the former being pre-

ferred. Chloromycetin is not usually used because of its bone toxicity.

The dose of tetracycline is 0.5 gm. orally/6 hrs for 10-12 days—for all other stages of syphilis excepting neuro-syphilis, where the therapy is continued for 20 days.

MERCURY

The only drug with mild trepanostatic effect which was available and used during all these centuries, in the prearsenic era. Hence the saying—'One night with Venus and three years with Mercury'. It had the added advantage of use, by all possible routes—inunction, oral and parenteral administration.

Antisyphilitic Preparations: (a) Calomel ointment 33 %, (b) Blue ointment or mercury oleate 1.3 to 4 gm. for inunction. (c) Injection of perchloride, biniodide and oxycyanide of mercury, I. M. injection, seldom used now.

Actions: Antisyphilitic action is negligible and it is unfit for sterilisation of the organisms. It may be used in late syphilis only, in which, active treatment is contraindicated.

Uses: Almost discarded, excepting in late syphilis and that also as an adjuvant therapy only.

POTASSIUM IODIDE

Transparent crystals of saline taste and soluble in water. *Dose:* 0.3—2 gm.

Actions: Besides its use in Lugol's solution for thyroid disorders, and as a stimulant expectorant, it finds its use in late syphilis, for dissolving fibrous and gummatous tissues. It does not possess any trepanostatic action. The *toxic* symptoms are produced in the form of *Iodism*, with gastrointestinal upset, increased secretions and skin rashes, which can be controlled by the stoppage of the drug and use of Fowler's solution.

Uses: (a) A stimulant expectorant but is contraindicated in acute stages.

(b) Lugol's iodine is used in thyrotoxicosis and goitre.

(c) Iodides are still-used in *tertiary syphilis* with complications of periostitis, arteritis, hydrocephalus and meningeal lesions, with mixed results.

ANTISYPHILITIC STATUS COMPARED

<i>Drug</i>	<i>Potency</i>	<i>Relative value</i>	<i>Special indications</i>
PENICILLIN	(a) Full potency. (b) All forms of syphilis. (c) Early stages specially.	(a) Drug of choice (b) Quick and prompt sterilisation (c) Negligible toxicity	(a) Early syphilis. (b) Syphilis of pregnancy. (c) Heredo syphilis (d) Social danger.
ARSENIC	(a) Same but slightly less potent and more toxic. (b) Not much used.	(a) Drug of choice in the past. (b) Same type of action but more toxic. (c) Early stages of syphilis, C. I. in late syphilis.	Same as above but used only if penicillin is contraindicated.
BISMUTH	Still less potent but helps in the consolidation of effect.	(a) Slow but prolonged action. (b) I. M. Use, (c) less toxicity than arsenic	Adjuvant to penicillin for consolidation of effect and prevention of neurorecurrence.
MERCURY	A weak drug. May be used in late syphilis only.	(a) Weak but a less dangerous drug. (b) May be used by all routes. (c) Late syphilis. (d) Nephrotoxicity.	Advanced syphilis and syphilitic eye lesions.
POTASSIUM IODIDE	Used only in the 3rd stage of syphilis and its complications.	Not an antisiphilitic but used in syphilitic complications for dissolving fibrosis.	Used for syphilitic gumma and aneurysm.

THERAPEUTIC CONSIDERATIONS

Syphilis is one of the most crippling disease in this world. The incidence of the disease is fairly high, may be exceeding even 10% in some country. About 5 lacs of fresh cases are reported every year, in U.S.A. 60,000 babies are born with heredosyphilis; 15% of blindness and 10% of insanity are due to syphilis.

Biological or radical cure, in which the patient is free from *treponema pallidum* completely, is possible only if correct diagnosis and appropriate treatment are prescribed from the very beginning. Otherwise,

in all *other cases*, only symptomatic relief is all that can be expected. Best treatment obviously means early diagnosis, efficient drug therapy, regular serological check up and avoidance of further exposures.

The treatment comprises: (a) *Treatment of attack* in the early phase of *primary syphilis* obtaining a negative W. R. reaction and (b) *Treatment for consolidation* or the maintenance of the effect of the antisyphilitic treatment in a manner that the patient remains completely symptom-free and also serologically negative, for all times.

In cases of *Early syphilis* one has to deal with (a) Resistant patients and resistant germs and (b) In *late syphilis* it is the patient and not the disease that should preoccupy the physician, as the patient's health is completely shattered.

Choice of drugs (a) Penicillin, (b) Bismuth, (c) Pot. Iodide.

Arsenic and mercury only in special cases of Penicillin intolerance, for the former, and late syphilis, for the latter. In actual practice, it is only *penicillin therapy* that counts, all the rest have served their time and been virtually discarded.

In the *pre-penicillin era* the standard method of treatment of early syphilis comprised the following:

(a) A series of courses (i), (ii), (iii), during which NAB and Quinostab were used, either alternatively or simultaneously: 10 weekly injections of the former and 12 weekly injections of the latter, in the *first course*.

(b) The *Second course*, starting on the 30th week had 5 weekly injections of NAB and 24 injections of bismuth.

(c) *Third course*, starting on the 71st week, comprised 5 weekly injections of N.A.B. and a *final course* of 12 weekly injections of bismuth, with an interval of 4 weeks rest period, between each course and a serological check up.

The entire course of treatment thus used to be of 92 weeks, comprising N. A. B.—20 injections and Quinostab: 48 injections. Or better still, mapharean, oxophenarsan or dichlorphenarsen: 0.5-1 mg/kg. or 40-60 mg. adult dose and Bi-subsalicylate: 0.2G, were considered satisfactory.

The *alternating course* protected the patients from cumulative toxicity, attacked the organisms from 2 directions and prevented the germs from becoming resistant or fast to the antisyphilitic therapy. The use of Bi with the first few doses of As, also lowered the incidence of neuro-recurrences.

STANDARD METHOD OF PENICILLIN THERAPY

Stage	Aqueous Procaine Penicillin	PAM	Benzathene penicillin
Primary, Secondary and latent syphilis	4.8 mega units (6 lac units/day for 8 days)	4.8 mega units (2.4 mega units in the first inj. and 1.2 mega units in the next two inj. at 3 days interval.	2.4 mega units in a single inj. If CSF is abnormal, 2.4 mega unit twice, at 3 days interval.
Asymptomatic or symptomatic neurosyphilis, late, gummatous and C. V. syphilis.	6-9 mega units (6 lac units/day for 10-15 days)	6-9 mega units (1.2 mega units/3 days in 5-8 inj. over 12-21 days.	6-9 mega units (3 mega units at 7 days interval i.e. 2-3 inj.)

In *late congenital syphilis*, same procedure as with neuro syphilis, is to be followed but the total doses to be reduced according to the body weight and age. Syphilis being the greatest *abortifacient*, even one out of six conceptions not being normally successful, active and energetic treatment of the prospective mother during conception, is essential. After active penicillin therapy, such children should be checked up by regular radiographic examinations of the epiphysis and also by regular paediatric check up. In *decompensated heart*, treatment of heart with digitalis and diuretics should be given first before anti-syphilitic therapy is started. The use of potassium iodide: 1-2 gm./tds. for 2-4 weeks, should also be considered in cases of gummatous and C. V. syphilis and also in syphilitic aortitis. For G. P. I., the use of *malaria therapy* has practically been discarded. For *syphilis of pregnancy*: energetic treatment before 6 months, with appropriate doses of 10 mega units of penicillin and 0.2 gms of Bismuth/week for 10 weeks, will safeguard the foetus.

Syphilis and Marriage: This is a problem of considerable social importance. Though the old dictum of 'once a syphilitic, always a syphilitic', is gone, vigilance and prudence are necessary. Regular medical surveillance, serological check up, elimination of chances of reinfection, are essential. If all is well, after sometime, marriage should not be interdicted to these potential dangers of the society.

Plate XXXV

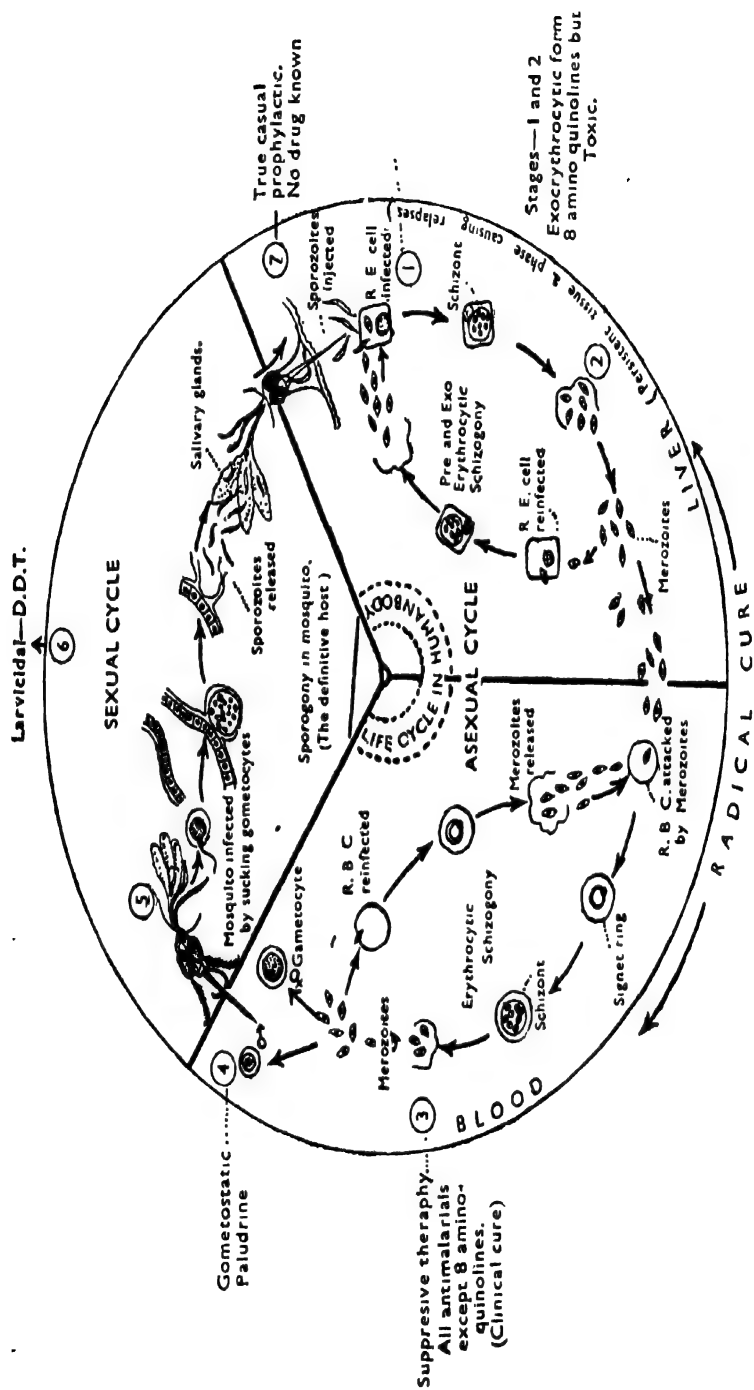
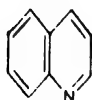
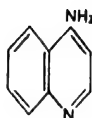


Fig. 97. Life cycle of *Plasmodium vivax* and site of action of antimalarial drugs

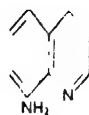
Plate XXXVI



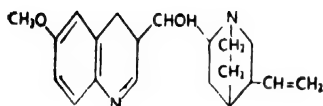
QUINOLINE



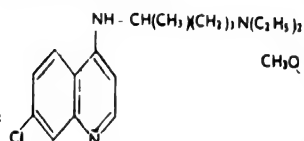
4. AMINO QUINOLINE



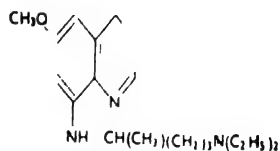
8 AMINO QUINOLINE



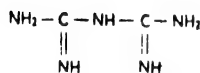
QUININE



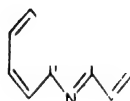
CHLOROQUINE



PAMAQUINE



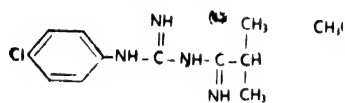
BIGUANIDE



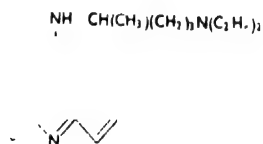
ACRIDINE



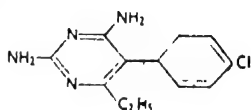
PYRIMIDINE



PALUDRINE



MEPACRINE



DARAPRIM

FIG. 98. Chemical structures of antimalarial drugs

CHAPTER

44

CHEMOTHERAPY OF PROTOZOAL AND OTHER PARASITIC DISEASES

PHARMACOLOGY OF (a) MALARIA (b) AMOEBIASIS (c) LEISHMANIASIS
(d) TRYPANOSOMA (e) FILARIA (f) SCHISTOSOMA (g) SPIROCHETES
(h) RICKETTSIA AND OTHER INFECTIONS. MODES OF TRANSMISSION AND
STATUS OF DRUG THERAPY

[A large number of protozoal and other parasitic diseases infest the tropical and subtropical regions of the world. These are malaria, amoebic dysentery, leishmania, trypanosoma, filaria and schistosoma infections, for the most of which, effective chemotherapeutic and control measures are now available.

The *antimalarial drugs* comprise quinine, 4 and 8-aminoquinolines, acridine, biguanide and other derivatives. With their judicious use, combined with control measures with D.D.T. or gammexane, it has now been possible to eradicate malaria, satisfactorily from most of the countries.

Of the *two types* of malaria, the *falciperum* induced *M. T. infection*, though fatal, is more easily amenable to cure with quinine and chloroquin, while the *Vivex* or *BT* infection, being more tenacious, requires 4-aminoquinolines-chloroquin and amidoquin for *clinical cure*, 8-aminoquinoline—primaquin and camoquin for *radical cure* and pyrimethazine for complete annihilation of the parasite from the body. The *current practice* comprises the use of quinine and mepacrine in M.T., chloroquin for B.T. suppression, premaquine for prophylaxis and D.D.T. for mosquito eradication.

Amoebic dysentery caused by *E. histolytica*, is endemic in India. It has a vegetative trophozoite and resting cystic form, causing intestinal and para-intestinal involvements. The *intestinal form* in the *acute phase*, is treated with emetine, followed by di-iodoquin, chloroxy-quinoline and also some of the broad spectrum antibiotics, amoebic liver abscess by emetine and chloroquine and subacute and chronic amoebiasis, by carbarson and vioform.

Filariasis: is another tropical condition due to *W. bancrofti*, inoculated by the mosquito culex. It produces repeated lymphangitis and elephantiasis. *Diethylcarbamazine* or hetrazan is the drug of choice. It may bring about radical cure if the treatment is started early. It acts on microfilaria, while suramine acts on the adult worms.

Leishmaniasis prevailing as kala-azar and tropical sore, has its specific therapy with urea stibamine, solustiboan, pentamidine and stilbamidine.

For *trypanosoma* infection causing yellow fever in Africa and South America, the therapy comprises the use of tryparsamide, butarsen, arsenic, antimony and diamidine compounds. Pentamidine is preferred in the early phases and tryparsamide in advanced cases. For *flagella* infections, mepacrine, acetarson, mapharside,

di-iodoquine, carbarson and aureomycin are used for *schistosomiasis*—trivalent antimony, for *guinea worm*—hetrazan and streptomycin and for lung and liver flukes, emetine and chloroquin ae used.]

CHEMOTHERAPY OF MALARIA

A remarkable advancement in the therapy of malaria, a disease previously considered to be associated with 'marshy land' the breeding place of mosquitoes, the word malaria denoting '*mal airia*' or bad air. A very old disease which had baffled the ingenuity of scientists for many centuries in understanding its nature of infection and mode of transmission. The discovery of specific drugs for this crippling disease occurred in two distinct periods—(a) The *quinine era* from 1633 to 1939 and (b) *Synthetic antimalarials*—first discovered in 1926 and used from 1939 onwards.

CLASSIFICATION

QUINOLINE DERIVATIVES:

Natural alkaloids:	Quinine.
8-aminoquinolines:	Pamaquine, pentaquine, isopentaquine & primaquine.
4-aminoquinolines:	Chloroquine and camoquine.

ACRIDINE DERIVATIVES: Mepacrine.

BIGUANIDO DERIVATIVES: Paludrine.

PYRIMIDINE DERIVATIVES: Daraprim or Pyrimethamine.

Chemistry: As shown in the table, the antimalarials belong to a large number of chemical groups. Amongst them, only quinine is a natural alkaloid and all the rest are synthetic compounds or their derivatives. Their chemical structures are shown in *Plate XXXVI: Fig. 98*.

Mode of Study: This is indicated in Chapter 6 and is carried out in the same manner as in the cases of other chemotherapeutic drugs. The method of evaluation comprises *toxicity* and *therapeutic efficiency* as well as, *clinical trials* of drugs on patients. Different laboratory animals can be inoculated with different strains of malarial parasites: (a) *Canaris* with *P. galictum*. (b) *Chicks* with *P. gallinicum* and (c) *Monkeys* with *P. knowlesi*. It is also possible to induce malaria in mice, as well. After inoculation, the peripheral blood counts are made and the action of unknown drugs compared with known standards.

Mode of Action: Due to our inadequate knowledge of metabolism of the malarial parasites and in the absence of culture techniques, the mode of action of antimalarials is not fully known. The following biochemical changes may subscribe, to some extent, to the nature of actions of antimalarials.

- (a) Cytochrome oxidase and glucose-6-phosphate dehydrogenase systems are depressed by mepacrine and quinine.
- (b) Oxidation of pyruvate to acetate through the tricarboxylic cycle, is inhibited by quinine.
- (c) Hexokinase and lactic dehydrogenase systems are inhibited by atebriene.
- (d) Porphoryn metabolism, connected with haematin uptake by the parasite, as well as folic and folinic acid utilisation, are interfered with by paludrine and daraprim.

Much more work is necessary for understanding the biochemical basis of action of different antimalarials, in different types of malaria, at different phases of evolution.

However, in spite of the present shortcomings, these drugs have been able to control one of the greatest Public Health Problems of India and Far Eastern Countries.

The credit of discovery of the malarial parasite goes to the eminent English parasitologist, Sir Ronald Ross and of the mode of transmission of the infection, to the French scientist, Laveran. This had led to the comprehensive knowledge of the disease, permitting the discovery of a galaxy of specific antimalarial drugs, by a number of workers for the last 125 years, as will be reviewed in the course of this study.

Life History: Though there are several types of plasmodia, the following are the important ones, for causing human malaria.

<i>Parasites</i>	<i>Duration of a sexual cycle</i>	<i>Clinical condition</i>
<i>P. vivax</i>	48 hours.	Benign tertian.
<i>P. falciparum</i>	48 hours.	Malignant tertian.
<i>P. malariae</i>	72 hours.	Quartan malaria.

In all these cases, man is the *intermediary host*, while the female anopheles, is the *definitive host*. The cycle of evolution of *P. vivax* is a typical one and occurs in the following stages: (Plate-XXXV; Fig. 97).

SPOROLOGY IN MOSQUITO	Zygote	SCHIZOGONY IN MAN	Sporozoites	Exo-erythrocytic (E.E.) phase.
	↓		Cryptozoites	
	Gametes		Merozoites	
	↓		↓	
	Gametocytes		Trophozoites	Erythrocytic (E.) phase
			Schizonts	

Sporozoites are inoculated into human beings by the anopheline mosquitoes. These rest in the reticuloendothelial cells of the liver for 1-2 weeks as '*erythrozoites*'. This is the *preerythrocytic or primary tissue phase*.

Some of these are then showered into the peripheral circulation as *merozoites*, which invade the erythrocytes and pass through the stages of *trophozoites* and *schizonts*. This is the *erythrocytic phase*. Others continue the cycle from *cryptozoites* to *schizont* in the liver tissue and this is known as *secondary schizonts*.

The antimalarial drugs which act on the *asexual erythrocytic phase* and destroy the trophozoites, removing paroxysms of fever, are known as '*suppressive drugs*'. It thus leads to symptomatic or clinical cure.

Some of the *merozoites* develop into *gametocytes*. These differentiate into male and female gametes and unite to form *zygotes* in the body of the mosquito and are finally inoculated in the form of sporozoites from the salivary gland of the mosquito, into human blood, thus spreading fresh infections.

The *Primary schizonts* developed from *cryptozoites*, continue multiplying in the liver, producing *Secondary schizonts* and periodically showering merozoites into the peripheral circulation, producing *relapses*. Drugs acting on this '*persisting tissue phase*', effect '*radical cure* and prevent *relapses*.

The *exoerythrocytic cycle* is persistent in the B. T. infection from 1-3 years, but usually dies off in M. T., after the initial paroxysm of fever. Hence relapses do not occur in this case. In *quartan malaria*, the *exoerythrocytic cycle* may last for 20 years.

Thus patients harbouring gametocytes, act as *carriers*. Drugs effective against these and preventing the development of sporozoites into primary schizonts, act as *casual prophylactics*, preventing further spread of the infection.

Types of Action: In this perspective of the life cycle of M.P., effects of antimalarials can be grouped under the following headings, though with certain overlappings.

1. *Causal prophylaxis*—affecting the pre-erythrocytic phase of M.P. as with primaquine, chloroguinide and pyrimethamine.
2. *Suppressive prophylactic*—affecting erythrocytic phase of development as with chloroquine, chloroguanide and pyrimethamine.
3. *Clinical cure*—affecting erythrocytic schizogony as by 4-aminoquinolines-chloroquin, amodiaquin.
4. *Radical cure*—by eradication of erythro and exoerythrocytic phases by 8-aminoquinolines—primaquine.
5. *Suppressive cure*—by complete elimination of parasites from the body with pyrimethamine.
6. *Gameto cytocidal effect*—by primaquine and chlorguanide. All these are diagrammatically represented in *Plate XXXV, Fig. 97*.

QUININE

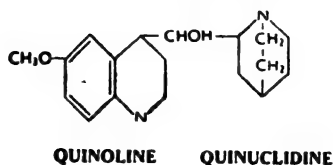
It is an alkaloid obtained from the cinchona bark, the anti-malarial property of which was discovered in 1633 after the cure of countless Annadale Cinchone of Spain. The plant was imported from Peru, named after her and introduced in Europe as an official drug.

Varieties	Total alkaloids %	Quinine %	Other crystalline alkaloids %	Isolated principle
<i>C. ledgeriana</i>	5.8	71.5	18.2	Quinine
<i>C. calisaya</i>	5.8	70.0	18.2	—
<i>C. succirubra</i>	6.1	28.6	54.2	Totaquine

Active Principles: The bark contains a series of alkaloids, acids, tannins and other substances. The alkaloids comprise : (a) l-rotatory—quinine and chinchonine. (b) d-rotatory-quinidine and cinchonidine.

Of these, quinine and quinidine are of pharmacological and therapeutic importance. The bark also contains quinovic and quinotannic acids.

Quinine was isolated for the first time by Pelletier and Caventou, in 1820 and its chemical nature observed to be as under:



Illus. XXIV. Quinolene and quinuclodine moities of the quinine molecule.

The quinine molecule contains one pyridine and one quinolene nucleus. It is a diabasic acid. The secondary alcohol linkage between quinolene and quinucleidine nuclei is essential for the plasmocidal activity. Its reduction increases the toxicity.

The neutral bihydrochloride salt is the most soluble, least irritant and suitable for I. M. injection and the SO_4 salt for oral use. The tennate salt is very little soluble and is devoid of the bitter taste of other salts. This also is the case with euquinine.

Incompatibility: lime water, ammonia, alkalies and metallic salts.

Preparations: Tincture and compound tincture of cinchona: 2-4 ml.

Cinchona febrifuge: 60-600 mg.

Quinine sulphate, bisulphate, hydrochloride and bihydrochloride: 0.3-0.6 gm.

Quinidine sulphate: 60-300 mg.

Metabolism: Quinine salts are absorbed from the small intestine as nascent alkaloid. The absorption is not much quicker after I. M. injection. The tennate and ethyl carbonate salts are more poorly absorbed. From the blood, quinine is distributed all over including the R. E. system. About 60% is destroyed in the muscle, liver and kidney and the remaining 40% is excreted in urine. The maximum excretion takes place in 3-10 hours and half clearance in 42 hours. It is detoxified by the process of demethylation.

Actions: These are of three types (a) Local, (b) Systemic and (c) Antimalarial.

Local: After an initial stimulation at low concentration, it acts as a universal depressant and protoplasmic poison affecting both the 'Brownian movement', as well as, fermentation process. It is also a local anaesthetic, analgesic and at the same time, a local irritant for mucous membrane and other tissues, causing nausea, vomiting, thrombosis and sclerosis of veins.

Systemic: It is an analgesic-antipyretic but the actions are less dramatic in cases other than malaria. The analgesic action is inferior to that of salicylates.

C. N. S.: There is stimulation of the special senses of hearing and sight and sometimes even convulsions.

C. V. S.: The action resembles quinidine but is much weaker. After I. V. injection, there is sometimes myocardial depression and fall of B. P.

G. I. tract: It is a bitter tonic but poor stomachic. It is also an irritant for the mucous membrane of the stomach. It is a stimulant of uterus but not an abortifacient unless very high doses are used.

Skeletal muscle: Quinine increases the tension response and the muscle tone, thus aggravating myasthenia gravis and relieving myotonia congenita.

Antimalarial action: This is not yet fully understood. Quinine has a *suppressant* action on the *erythrocytic*, as well as *pregametocyte phases* of the B. T. and *curative* action on the M. T. infection. It has no action on sporozoites. It can precipitate an attack of 'black water fever', if used intermittently. This does not occur with chloroquin or mepacrine.

Cinchonism: It is a combination of allergy, irritation and specific toxicity, resulting in (a) G. T. upset, (b) mental confusion and headache, (c) cardio-respiratory depression and (d) even middle ear and retinal changes.

Its *management* comprises the use of (a) $MgSO_4$ purgative, (b) Adrenaline, (c) Nitrites for visual troubles, (d) Bromides for tinnitus aureus.

Uses: Besides malaria it is sometimes used as:

- (a) Analgesic-antipyretic.
- (b) Sclerosing agent: 5% solution of quinine + urethane for varicose veins.
- (c) Delivery cases, only with ergot.
- (d) Contraceptive and hair tonic.
- (e) Diagnosis of myasthenia gravis, the condition being aggravated.
- (f) Myotonia congenita: 0.3-0.6 gm./day. The drug may sometimes cause dramatic relief bringing the electric reactions of the muscles to normal again, temporarily.

PAMAQUIN

Also known as plasmoquin, is an 8-amino-quinoline derivative, synthesised by Schulemann, starting with methylene blue.

Tasteless, orange-yellow powder. *Dose:* 20-36 mg. The HCl salt is available as tablets of 10 mg., 2 tabs. t.d.s. It is readily absorbed producing peak concentration in 2 hours. It is partly excreted in urine, to the extent of 1% only.

Toxicity: It is a toxic drug with low safety margin, producing G. I. upset, tachycardia, haemolytic anaemia, meth-haemoglobinaemia and liver damage. It is not therefore much used these days and has been replaced by its congeners: penta and isopentaquins.

Actions: It is 60 times more potent than quinine in avian malaria, acting mostly on the *gametocytes* and the *tissue phases* of the parasite. It is useful only for the prophylaxis and prevention of relapses. It has insignificant action on the sexual form of the malarial parasite and is thus useless in acute attacks.

Pentaquine: Another 8-aminoquinolene derivative and a variant of pamaquin. The disodium salt, in doses of 30 mg. with 2 gm. of quinine/day, in divided dose/4 hr is used. Its metabolism and toxicity are of the same type as for pamaquine. It has specific action on the erythrocytic tissue phase of the *P. vivax* and it effectively prevents relapses. It has very slight action on the erythrocytic form of the parasite and is not therefore suitable for acute attacks of malaria. It is on the whole, less toxic clinically than pamaquine but primaquin is much better and more used these days for the radical cure of B. T., along with quinine or better still, a 4-amino quinolene compound. The drug may occasionally give orthostatic hypotension from its central sympathetic effects.

Isopentaquin: Another 8-aminoquinolene derivative and is also effective in relapsing *vivax* infections. *Dose:* 30 mg., in combination with quinine. It is less toxic but 20-30 times more potent than pentaquine.

Primaquin: It has got the common characteristics of 8-aminoquinolene derivatives. In doses of 10-15 mg./14 days, it can effect radical cures of relapsing B. T. infections. The drug may however sometimes cause abdominal cramps, anaemia and cyanosis but this does not usually occur even in 14 days therapy. Amongst the 8-amino quinolene compounds, this is the most promising and effective drug for the radical cure and is used along with chloroquine, in B. T. infection. It is much better than pamaquine and the cure rate is over 99% and its therapeutic coefficient the highest amongst the antimalarials.

CHLOROQUINE

Also known as *resoquin*, it is a chlorinated 4-aminoquinolene compound which is readily absorbed but slowly excreted. It is concentrated

in the nucleoprotein of the R. B. C. and also in the liver, which probably explains its schizonticidal action.

Toxicity: Usually negligible in man, though as much as mepacrine, in animals. It causes occasional lichencid type of dermatitis, blurring of vision, diplopia and depression of T wave. However, ordinarily, it is a safe drug in the therapy of malaria.

Action: It is one of the most potent *suppressives* of the B. T. and M. T. infections acting mostly on the erythrocytic form. The patient becomes afebrile in 24-48 hrs. The drug has no action on the exoerythrocytic form of the P. vivax. Its advantages are quick action, less relapses, low toxicity and ease of administration. *Dose:* 0.6 gm.—0.3 gm. and then 0.3 gm/daily for 2 days for suppression, and 0.3 gm/week, for the purpose of prophylaxis.

Other Uses: (a) Hepatic amoebiasis (b) Tape worm infection (c) Lupus erythematosus (d) Antiarrhythmic use (e) Hypersensitivity reactions (f) Giardiasis (g) Leishmeniasis.

Amidoquin: It is another 4-aminoquinolene derivative having similar actions to chloroquin. It adequately suppresses the B. T. and M. T. infections, sometimes even by a single dose of 800-1200 mg. It is available as hydrochloride salt, in the form of tablets of 200 mg. each. Like chloroquin, it is also used in amoebic hepatitis but not in intestinal amoebiasis.

Camoquin: A variant of chloroquin and several times more potent. It is much less toxic than mepacrine. A single dose of 1 gm. may completely eliminate B. T. and M. T. parasites. Though usually nontoxic, it may sometimes produce (a) G. I. upset and (b) Insomnia.

MEPACRINE

Atabrine, a 8-aminoacridine derivative, introduced by Schulemann in 1930 after screening 12,000 compounds. The dihydrochloride salt is bitter and yellow powder. *Tablets:* 100 mg. 2 tabs/day for 5 days, followed by 1 tab. t.d.s. for 7 days; 3% sol. I. M. & 100 mg./day.

Metabolism: It is readily absorbed and stored in R. E. S. It diffuses in foetal blood, C. S. F. and erythrocytes and is slowly excreted in urine, bile and faeces.

Toxicity: (a) Yellow colouration of skin in 50% of cases, clearing up in 10-15 days. Secretions also may be stained but the sclera remains clear. (b) Nausea, vomiting, headache and transient psychosis. Also occasional dermatitis, hepatitis and anuria.

Actions: (a) It is a suppressive in B. T. and curative in M. T. infections and its actions are stronger than those of quinine. It has hardly any action on gametocytes or e.e. forms.

(b) Its inhibitory action on cholinesterase and antifibrillatory action are faster than quinidine.

(c) Its actions in tape-worm, giardia and lamblia infections and also dermal leishmaniasis and erythematosis, are appreciable.

Special Advantages: Compared to *quinine*, the drug presents several advantages in antimalarial therapy: (i) Less unpleasant taste (ii) shorter course of therapy (iii) Less toxicity (iv) No cinchonism (v) No oxytotic action and finally (vi) No C. I. in black water fever.

PALUDRINE

A biguanide derivative, introduced by the British School of workers in 1944 during World War II.

(a) Paludrine is chlorguanide acetate and

(b) Proguanil is chlorguanide HCl. *Dose:* Tabs. 100 mg. b.i.d. or t.d.s.

The acetate salt is suitable for injections.

Metabolism: (a) Rapid absorption and excretion and yet infrequent doses. (b) 50% excretion in urine and only a trace after a week.

Toxicity: Insignificant: (a) Epigastric distress, vomiting and diarrhoea (b) Hypersensitivity reaction (c) Occasional haematuria.

Actions: (a) Suppressive in M. T. and B.T. and prophylactic in M. T. infections. (b) It has no action on the tissue phase and gametocytes but *resistance formation* in E & E. E. forms.

Uses: Acute attacks of M. T. and B. T. infections, action slower than quinine and chloroquin. In *falciparum* infection, considered to be a

casual prophylactic, suppressive and curative. In *vivax* infection, is not better than chloroquin and in giardiasis, atebine is preferred.

In *substance*, though the drug had a high reception when it came into the field, during the war, excepting as a prophylactic in M. T. infested areas, it is very little used in actual practice, due to its side-effects.

DARAPRIM (PYRIMETHAMINE)

It is a pyrimidine compound, which was initially believed to be of promise as a suppressive in both B. T. and M. T. infections. It is a potent antimalarial, a single dose of 0.5 mg/kg. of which, was found to be capable of removing the schizonts and the trophozoites from the peripheral blood of the patient in 48-72 hours. Further, being a tasteless drug, it was also found to be suitable for use in children. The drug acts mostly on the *asexual* erythrocytic phase of all forms of malarial parasites and though it has no action on the tissue and gametocytic phases, it makes sporozoites non-infective for mosquitoes. The drug was found to disturb the utilisation of folic and folinic acid by the parasites. However, human responses to the drug after clinical trials, soon revealed that the compound caused dangerous bone marrow depression and *agranulocytosis*, a point which was not revealed by animal experimental studies. The drug had therefore to be withdrawn from the market, because of its gross toxicity hazards.

ACTIONS COMPARED

<i>Locus of action</i>	<i>Asexual erythrocytic phase</i>	<i>Persistent tissue phase</i>	<i>Action on gametocytes</i>
<i>P. vivax.</i>	Chloroquin Mepacrine Quinine. Quinine	Chloroquin with Pamaquin or Primaquine. Quinine	Paludrine, Daraprim, Pamaquine, Primaquin. Pamaquine and Primaquine
<i>F. falciparum.</i>	Mepacrine Chloroquin Chloroquin	Mepacrine Paludrine Paludrine Chloroquine	
<i>Nature of action</i>	Clinical cure	Radical cure	Prevention of spread, causing causal prophylaxis

THERAPEUTIC CONSIDERATIONS

Until recently, malaria has been one of the most crippling diseases in the world with its high mortality and morbidity, chronic anaemia and

debility and colossal loss of working hours, in the effectual population.

Millions of fresh cases are reported every year and India's share is about 50%. During presynthetic antimalarial era—only 600 tons of quinine i.e. 50% of actual requirement of the world was available and India's quota used to be 10% only, of that.

With the synthesis of newer antimalarials and vigorous anti-malarial campaigns with drugs like D.D.T., the situation is much under control now but the fear of resistance formation of mosquito and M.P., cannot be ruled out. Further, variable responses of host and parasite, according to types and stages of evolution, are real hurdles in the effective planning of cure and eradication programmes.

Further, the reproduction rate of M. P. is terrific. One scizont gives 24 in 48 hrs., 250 millions or 50 m.p./cc. of blood in 14 days and the next generation, after 48 hours, gives a paroxysm.

If a drug destroys 96% of these parasites, only the equilibrium is maintained, but not cure. This proves how powerful an antimalarial action is required of these drugs.

In the present state of our knowledge, malaria cannot be treated only by one particular drug but at least 2-3 drugs are to be used in their respective places, singly or in a group, for effective control of malaria.

Standard Army Method: During World War II, for all types of malaria.

<i>Drug</i>	<i>Dose</i>	<i>Days of Treatment</i>
Quinine	0.6 gm. t.d.s.	1, 2
Mepacrine	0.1 gm. t.d.s. p.c.	3, 4, 5, 6, 7.
Nil	—	8, 9,
Pamaquin	20 mg. morning and 10 mg. evening.	10, 11, 12, 13, 14

This method could not take into consideration the latest drugs and today, antimalaria therapy is planned in the following manner:

B. T. Malaria: Chloroquin (resochin)—250 mg.—4 tabs—2 tabs. after 12 hrs. and then 2 tabs/day for 13 days, followed by primaquine: 7.5 mg. base or 12 mg.—2 to 3 tabs/day for 3-4 days. One more course may have to be given.

M. T. Malaria: Irrespective of the clinical form—cerebral, hyperpyretic or algid, the line of treatment should be—quinine 0.6 gm.

I. V. or I. M., with usual precautions, followed by oral quinine or mepacrine, followed by camoquin 250 mg./O.S. t.d.s. for the next 2-3 days and thereafter, once a day, for a week.

Chronic Malaria: Camoquin—1 tab. twice a week for 3 months and fersolate-2 tablets b.d. for a month or two.

Malaria of Pregnancy: All other antimalarials except quinine, can be used.

Chronic Hepato-Splenomegaly: iron, arsenic and sometimes a provocative dose of adrenaline 0.5 c.c. for 2 days, for inducing splenic contraction, exposing m.p.s. to drug action.

From this *short review*, it is apparent what great strides have been made in the control of malaria during the last few decades. Even in the early thirties of the century, there was only one antimalarial of importance in *quinine*. Two more—*plasmoquine* and *mepacrine* were then added and during the last 3 decades, tremendous advances in the discovery of specific drugs, almost to *tailor fit* the disease, with so many potent agents, has been made. Of these, the role of (a) Quinine and mepacrine in M. T. infection, (b) Chloroquine in B. T. suppression (c) Primaquine and other 8-aminoquinolines in prophylaxis and (d) D. D. T. for eradication, cannot be lost sight of. However, while hardly these advances are in progress, one is already faced with the disconcerting problem of drug resistance of M. P., as well as of the mosquito. This no doubt is the usual challenge to scientists who as in the case of antibiotics, will know how to solve or circumvent it, with his ingenuity of research, enabling the progress to continue, as always.

CHEMOTHERAPY OF AMOEBIASIS

Another tropical disease with wide geographical distribution, India's share being very high and the disease prevailing in endemic form all over the country. (Plate XXXVII; Fig. 99).

The causative organism in *Entamoeba histolytica*—a unicellular multinucleated parasite, multiplying asexually in colon. Its toxic secretion affects the mucosa and causes shallow ulcerations, colitis and dysentery. The infection takes place through foecal contamination of food.

The vegetative *tropozoite*, after producing acute dysentery, assumes *resting cystic* form, which produces bridge heads and infiltrate

Plate XXXVII

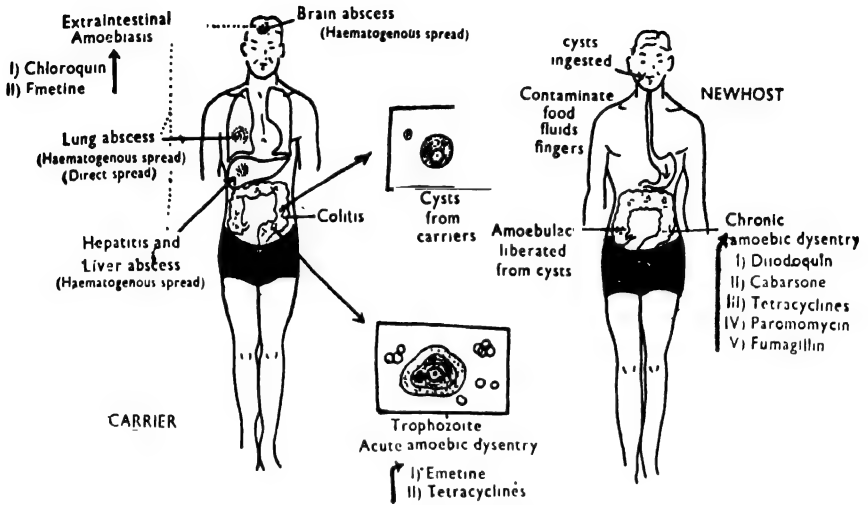


FIG. 99. Mode of infection with *E. histolytica* and actions of amoebicidal drugs

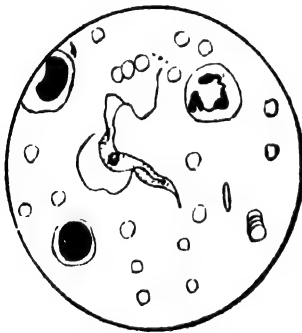


FIG. 100. *Trypanosoma gambiense* causing sleeping sickness



FIG. 101. *Tryponema pallidum* causing syphilis

into liver, lungs and brain. The vegetative form is accessible to treatment, while the cystic form is responsible for chronicity, transmission of infection and is very much resistant to drug action.

The discovery of an *ideal* antiamoebic drug is therefore not easy, inasmuch as it (a) should kill or arrest the growth of the vegetative form (b) hinder its migration and (c) also deal with the cystic form of the amoeba.

- Evaluation:** (a) By in vitro culture, free from symbiotic bacteria, requiring special culture media.
 (b) Experimental amoebiasis in *Macus rhesus monkey*, rats and kitten by inoculation of the large intestine with laboratory culture.
 (c) Clinical assessment by repeated stool examination and sigmoidoscopy.

CLASSIFICATION

Emetine—Kurchi group

Emetine, E.B.I., K.B.I.

Organic arsenicals.
 4 & 8-amino quinolines.

Carbarson, Acetarsone and Milibis.
 Chloroquin, Camoquin and Di-iodoquin.

Antibiotics.

Terramycin, Aurcomycin, Fumagilline, Bacitracin, Erythromycin & Penicillin.

EMETINE

The isolated alkaloid of *Cephaelis ipecacuanha*, growing in Brazil. It is *methyl cephaline*, an isoquinoline compound, isolated by Pelletier and Magendie, in 1816. *Dose*: Emetin HCl 30-60 mg. S. C., I.M.

Metabolism: Poor absorption, partial destruction, irritation and even *emesis* on *oral administration*. The excretion is slow, traces upto a month, through kidney and even stomach. It is a *cumulative poison*.

Actions: (a) A local irritant, protoplasmic poison and also a bitter stomachic, emetic and reflex expectorant. (b) An important C. V. depressant, affecting the myocardium and B. P. with definite E. C. C. changes. (c) *Amoebiacidal action*—first discovered by Rogers in 1912, in a concentration of 5×10^6 , which is attained in the body, in thera-

peutic doses. It is effective only in about 40% cases and relapses in the rest. It does not affect the cysts.

Toxic Effects: (a) Nausea, vomiting and diarrhoea, (b) Inversion of T. wave (c) Peripheral neuritis and haemorrhagic rashes (d) A dose of 0.5 mg., is definitely lethal.

Uses: (a) Acute amoebic dysentery and also (b) Amoebic hepatitis.

PENTAVALENT ARSENICALS

Acetarsone or stovarsol: Tablets of 0.25 gm. b.i.d. or t.i.d. for 10 days, in subacute and chronic cases. Use almost discarded now because of toxicity.

Balarsen: The arsenoxide form of acetarsone, combined with BAL, in the name of *Balarsen*. It is highly effective in *intestinal amoebiasis* and is also nontoxic. *Dose:* 10 mg/kg/OS for 5 days.

Carbarsone: It is fairly effective on cystic and vegetative forms and has negligible toxicity. *Dose:* 0.25 gm. b.d/O.S./7 days, repeated after one week. *Retention Enema-2* G/200 ml. of 2% bicarbonated water, is also used in acute amoebiasis.

OXYQUINOLINE DERIVATIVES

Chiniofon: An iodoxy quinoline compound introduced by Mhulens in the name of *Yatren*. It contains 27.5% of iodine.

It has a direct amoebicidal effect due to the presence of the quinoline moiety, on the vegetative and cystic forms, in intestinal amoebiasis only. *Dose:* (a) Enteric coated tablet of 0.25-1 gm. t.d.s. (b) Retention enema—6 gm/300 ml. of warm water, every night, for 10 days.

Toxicity: Negligible but sometimes—(a) Profuse diarrhoea, (b) Iodine intolerance and (c) Liver damage.

Uses: (a) Subacute and chronic amoebiasis, (b) Treatment of carriers, for which, it is alternated with carbarsone.

Vioform (Enterovioform): Iodochlorohydroxy quinoline, containing 42% of iodine. It is absorbed from the G. I. tract, detoxified in the liver and excreted in urine. It is contraindicated in hepatic damages.

Dose: Enteric coated tablets of 250 mg. t.d.s. for 10 days. It is most widely used with apparent good result, and sometimes even abused.

Diodoquin: A synthetic 8-quinolene derivative, containing 64% of iodine. At a concentration of 45/ug%, it produces amoebistatic action and is very effective in intestinal, as well as, systemic amoebiasis. It is superior to chiniofon in this respect.

Emetine and di-iodoquin combination gives better results than emetine and carbarsone—in acute amoebiasis, for the prevention of chronicity. It is also used in 'lambliasis' and balantial dysentery. *Dose:* Tablets of 0.65 gm/O.S./t.d.s., for 10 days.

Chloroquin: Introduced as an anti-amoebic drug in 1949, it has no effect on the intestinal trophozoites but is a better substitute for emetine in amoebic hepatitis, though the mechanism of action is not yet fully understood. It is 600 times more concentrated in the liver and yet it has negligible toxicity. The diphosphate salt is used in the form of 250 mg. tab.

Camoform: (biallylamicol hydrochloride)—an orally effective amoebicide, active against both intestinal and extra intestinal amoebiasis. *Dose:* 1-2 tablets/t.d.s. for 5 days.

Milibis: Also known as *glycobismarsolamine*, containing 15% arsenic and 42% bismuth. *Dose:* 0.5 gm/t.d.s. for 7 days/orally.

It is an active amoebicide for intestinal amoebiasis. It is relatively atoxic.

Entamide: (diloxamide): a synthetic compound with higher amoebicidal activity both *in vivo* and *in vitro*. *Dose:* 10 mg/kg/O.S./daily for 7 days. *Mexaform* (vioform + entamide 2 tab. t.d.s. or *plain furmide* is also used.

ANTIBIOTICS

The antibiotics also play some role in the management of amoebiasis. Some of them like *fumagillin*, possess antiamoebic activity, while others like *penicillin* are used as an adjuvant therapy, along with specific antiamoebic drugs, for disturbing the symbiosis of intestinal flora.

After the introduction of the micromanupulation technique of Reese, it has now become possible to culture the amoebic cyst in pure forms and also study the symbiotic action of gram positive organisms on them, in the intestine. As a result of these studies, the following facts about the efficacy of antibiotics in amoebiasis, has been established,

- (a) *Fumagillin* and *bacitracin*, obtained from *streptomyces* and *P. subtilis*, have direct specific amoebicidal action at a low concentration, attainable with a dose of 20 mg. t.d.s. for 10 days.
- (b) *Penicillin* and *streptomycin* are effective for disrupting the symbiosis of *entamoeba histolytica* with other intestinal flora by controlling the secondary organisms in the intestine.
- (c) *Tetracyclines*: terramycin and erythromycin are also effective in intestinal amoebiasis from their direct and indirect actions and so also is puramycin in a dose of 5-50 mg/kg/I.M.

TREATMENT OF AMOEBIASIS

It is an important 'Public Health' problem in India, due to its (a) high incidence (b) tenacious and often silent courses and (c) polymorphic nature, not controllable by any single drug.

Management of amoebiasis, consequently, comprises different measures of therapy, according to different stages.

- (a) Treatment of acute, sub-acute and chronic intestinal conditions.
- (b) Treatment of paraintestinal amoebic complications.
- (c) Treatment of carriers.

Regular checkup by *stool* examination and in all cases of chronic colitis, history of earlier amoebiasis, are very important.

Acute Attack: (a) *Emetine HCl*—60 mg. I.M./day for 6 days, preceded by penicillin 3 lac./units/day, for 2 days and an alkali mixture or alternately, one of the broad spectrum antibiotics, for disturbing the symbiosis.

(b) During emetine therapy—*diodoquin*—180 mg.—2 tabs/t.d.s. or chloroxy-quinoline—siosteron compounds, should be given.

(c) *Broad spectrum antibiotics*—aureomycin, terramycin, fumagillin and bacitracin—2 gms. daily/divided doses/for a week, combined with diodoquin, reduce the relapse rate.

Amoebic Abscess: (a) Though emetine has long been used, *chloroquin* is the drug of choice today. 1 gm/day for 2 days—0.4 gm/day for 14 days, is the normal schedule of treatment.

(b) Paraintestinal amoebiasis should also have the concurrent treatment of intestinal amoebiasis. Arsenicals and oxyquinolines should not be used because of their hepato-toxicity, besides their inefficacy in this condition.

Subacute and Chronic Amoebiasis: (a) Emetine is useless, excepting for acute exacerbations. *Diiodoquin*, carbarsone, *vioform* and bismuth derivatives are more frequently used,

Treatment of Carriers: Emetine is useless and drugs like *carbarsone* and *chiniofon*, are used for the cystic forms in chronic cases.

CHEMOTHERAPY OF LEISHMANIASIS

This is a tropical and subtropical disease, prevailing in India and mediterranean regions and produced by—(a) *L. D. Body* and (b) *Leishmania Tropica* respectively, the first producing the well-known *Kala azar* of India, with hepatosplenomegaly, typical paroxysmal fever, pigmentation of skin, leucopenia and haemorrhagic tendencies. Early diagnosis is made by examination of peripheral blood and marrow smear. It usually had a chronic but fatal termination, which prognosis, has considerably changed from the time of the discovery of specific drugs. The *second* produces oriental or tropical sore and also leishmaniasis in the mediterranean regions, of less virulence than *Kala-azar*. The infection takes place through a *sand fly* (*Phlebotomus argentipes*), which is the intermediary host.

Specific therapy comprises the use of a (a) Antimony preparations (b) Stilbene derivatives (c) Berberine and (d) Mepacrine.

ANTIMONY

Historical: A very old drug, used from the time of Dioscorides, for all imaginable diseases and introduced as *triumphant chariot of antimony*. It derives its name from *antimoine*, from its catastrophic effects on starved and emaciated monks, for whom, it was once used for producing fattening effect. This anecdote has not been fully substantiated.

Chemistry and Preparations: They resemble arsenic in many respects. The preparations are derived from *phenylstibamic acid*.

Inorganic

Oxide and chloride salts—too toxic for use.

Preparations	Uses	Toxicity
Tartar emetic, Stibo-phen, Anthiomalin, Thioglycollate	Fillariasis, Bilharziasis, Expectorant, Tropical sore, Schistosomiasis, Granuloma inguinale.	+++
Trivalent. Thioglycollamide.		

Organic

Pentavalent. Solustibosan, Neostibosan, Urea stibamine.	Kala azar and also Oriental sore.
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Metabolism: Antimony preparations are slowly absorbed and excreted. They are accumulated in the reticulo-endothelial system. The *trivalent* preparations are excreted in the gut, while the *pentavalent* ones, in the urine. The metal presents cumulative toxicity like others.

Toxicity: Antimony produces universal depression of the skin, mucus membrane and also some of the vital organs. There may be: G. I. upset, arthralgia and jaundice. During antimony therapy, as in leishmaniasis, (a) Pulmonary complication (b) Cardiac depression and (c) Anaphylactic reactions, have been observed. The injections are therefore to be given with the same precautions as is followed for organic arsenicals, the patient in empty stomach and lying down in bed. The *management* is similar to that for arsenicals: (a) Withdrawal of the further administration of the preparation. (b) Supportive therapy and (c) use of B. A. L.

Actions and Uses: Both the trivalent and pentavalent forms are used in therapeutics.

Tartar-emetic: or Sodium-potassium antimony tartrate. The *emetic dose:* 30-120 mg. and the *expectorant dose:* 2-8 mg. Trivalent antimony is not used in leishmaniasis but sometimes used in oriental sore as 1-2 per cent ointment, for lymphogranuloma and bilharziasis. The dose is 30-120 mg., 6% solution, 12 injections on alternate days.

Stibophen: It is much less toxic than tartar emetic and is used in schistosomiasis and lymphogranuloma inguinalis, in gradually increasing doses 1.5-5 ml., 12 I.M. injections.

Thioglycollate and thioglycollamide: Dose 50-100 mg. 15-25 injections. Anthiomalin, solustibosan and neostam have also been used in varying doses, by I.M. or I.V. injections, in cases of filaria, bilharzia, leishmania and lymphogranuloma infections.

Neostibosan and Ureastibamine: 5% solution 50-300 mg., I.V. 8-10 injections, on alternate days and 2% solution 50-300 mg. 20 I.V. injections, two to three times per week, respectively. These are the drugs of choice today for the treatment of Kala-azar, some preferring neostibosan and others ureastibamine. With appropriate therapy, the mortality rate has been reduced from 92 to about 20% only.

Stilbene derivatives: There are several of them—stilbamidine, propamidine and pentamidine. They are used in doses of 1.5—5 ml. (10% sol.) in leishmania and trypanosome infections with varying results. They are toxic substances, producing tachycardia, allergic and neurological troubles.

Berberine sulphate and mepacrine: These drugs are also sometimes

used in 1-2% and 10% solution respectively, in *oriental sore* and dermal leishmaniasis, with some benefit.

THERAPEUTIC CONSIDERATIONS

This will be discussed under the two heads (a) management of Kala azar (b) management of oriental sore or dermal leishmaniasis.

Kala azar: There are two aspects in the management of Kala azar: (a) Prophylactic (b) Curative.

Prophylactic: Though not fully satisfactory, D.D.T. spraying and besmearing of the skin with dimethyphenolate and also use of mosquito net against the sand flies, are recommended.

Curative: The drugs of choice are (i) *ureastibamine* and *neostibosan*, which are considered to be specific for this condition. Any one of them may be useful in gradually increasing dosages, particularly with due precaution against reactions and toxicities. The ranges of their doses and mode of administration have already been indicated. (ii) *Neostan* 100 mg./ml. I.M. or I.V. 6 injections. (iii) *Stilbimidine* 2 mg./kg. I.M. or I.V. for 12-15 days.

Oriental sore: Here again the treatment is local, as well as systemic.

Locally application of CO₂ sticks, phenol, x-ray and radium therapy, is advocated. *Curative:* (i) *Neostam* 2% solution, at weekly intervals (ii) *Berberine sulphate* 2% solution/2 ml. and (iii) *Emetine hydrochloride* 5% sol/2 ml., may be tried.

CHEMOTHERAPY OF TRYPANOSOMIASIS

A dangerous disease, endemic in Africa and South America and produced by the bite of *Tsetse* or *glossina palpalis* type of flies, which are the vectors of *T. gambiense* (Plate XXXVII: Fig. 100) *T. Rhodensis* and *T. Curzi*. The infection is taken by the flies from big games and the cycle is completed in their bodies and finally transmitted in man through the salivary secretions of the fly. The disease is characterised by fever, enlarged cervical lymph glands, oedema of legs and neurological disorders-tremors and C. S. F. changes, in late stages. The laboratory diagnosis comprises the lymphnode and peripheral blood smear examinations.

Drug Therapy: This comprises the use of:

(a) Arsenicals—atoxyl, tryparsamide and butarsen,

- (b) Antimonials—tri- and pentavalent preparations.
- (c) Diamidine compounds—stilbamidine and pentamidine.
- (d) Antibiotics and antrycide.

Atoxyl: Its use has now been discarded because of its retinal toxicity. The sodium salt of trypanasamide 1-2 gm. I.V. has adequate diffusion in the C. N. S. and is used for this, as well as, for neurosyphilitic conditions.

Butarsen: A butyric acid derivative of the trivalent arsenic 0.5 mg/kg/day/2 weeks. It is less toxic, quick acting and useful in early and resistant cases.

Stilbaimidine: 1 mg/kg/day/2 weeks in combination with pentamidine, used for early, as well as, advanced cases.

Further, *antibiotics*—streptomycin, erythromycin, puromycin and achromycin, are also of some value in this condition.

Trypanasamide: It is a pentavalent arsenical, used for the treatment of trypanosomiasis. It is given I.V. in doses of 2 gm. in 10 ml. of water, to a total of 10-12 injections at an interval of 5-7 days. The drug is toxic and causes G. I. disturbances, liver damage, dermatitis, Herxheimer's reaction, nitritoid crisis and optic atrophy, due to which the drug is used with certain amount of restrictions and in very aspecial conditions only.

Suramin: or Bayer '205', is a complex derivative of urea and is effective in African trypanosomiasis but not in advanced cases, where there is involvement of the C. N. S. Special points about its metabolism and actions are: (a) binding in tissue proteins, (b) slow release, (c) reabsorption by the tubular epithelium of the kidneys and (d) inhibition of anaerobic glycolysis. Its *side-effects* are nausea, vomiting, diarrhoea, skin rashes, fever and allergic hypersensitivity. *Dose*: 1 gm. initially I.M., to be repeated. The drug however is not frequently used.

Milibis: a commonly used drug which is effective in advanced cases of sleeping sickness and also in cases where there is involvement of the C. N. S. Its side-effects which are frequent, are—vomiting, diarrhoea, abdominal pain, dermatitis, allergic reactions, encephalopathy and cardiac damage. *Dose*: 0.5 gm. for 1 week, at 6 hourly interval.

THERAPEUTIC CONSIDERATIONS

The management of trypanosomiasis is complex and not fully satis-

factory. It comprises both *prophylactic* as well as *therapeutic* measures, the latter differing again in *early* and *advanced* cases.

Prophylactic: (i) destruction of big games in endemic areas. (ii) compulsory treatment of all natives. (iii) spraying of D.D.T.

Curative: Early cases: (a) I.M. or I.V. *pentamidine* 10% sol. 100 mg. I.V. daily for 10-20 days or 100 mg. I.M. *first day* and 200 mg. subsequently, for 9 days. (b) *Anthisan:* 100 mg. before injection.

Advanced cases: (a) *tryparsamide* I.M. or I.V. 1-3 gm. in 10 ml. water, every week, till a total of 20-100 gm. is reached. (b) *Milibis* 3.6 mg/kg. in propylene glycol, I.V. for 4 days.

ANTIFLAGELLATE AND ANTICILIATE DRUGS

Giardiasis: It causes dysentery like symptoms in children and is improved by *mepacrine* 100 mg. t.d.s. for a week. For children, the dose is 1/6th of this.

Trichomoniasis: It produces vaginitis with irritation and itching, which is treated with *acetarson* and *mapharside* insufflations and also by *aureomycin* dusting. Lactic and phosphoric acid douches are also sometimes useful.

Balantidiasis: It resembles amoebiasis and is treated with *diiodoquin*, *carbarson* and *aureomycin*.

CHEMOTHERAPY OF FILARIASIS

A major social and economic problem in the tropic and it has been estimated that any one time, there are more than 20 million cases of this disease. It is caused in man by *W. bancrofti*, *W. malayi*, *loaloa* and *O. volvulus*. Infection with *W. bancrofti* is common in Central Africa, South America, India and Southern China.

Drugs are used in this condition for (a) killing the microfilariae, (b) sterilizing the adult worms and (c) preventing or reducing the allergic symptoms, due to the destruction of worms.

The drugs commonly used are *diethylcarbamazine* and *suramin*.

Diethyl Carbamazime: Also known as *hetrazan*, is the most effective antifilarial drug, introduced by Hewitt and coworkers, in 1947. It is rapidly absorbed from the G. I. tract and the peak blood level is reached in 3 hours. It is uniformly distributed in the body and is entirely excreted in urine in 48 hours,

Actions: It causes rapid disappearance of the microfilariae of *W. bancrofti*, *W. malayi* and *loalca* from the blood by sensitizing the microfilariae to the phagocytic action of the microphages of reticulo endothelial system. It also causes the disappearance of microfilariae of *O. volvulus* from the skin but does not kill them in the nodules. It kills adult worms of *W. malayi*, *loalca* and probably also of *W. bancrofti*, but has little action against the adult *O. volvulus*.

Preparations: Diethylcarbamazine citrate-tablets of 50 mg. and syrup 30 mg/ml. For *W. bancrofti* and *W. malayi*: 2 mg/kg. t.d.s. after meals for 3 weeks. (b) For *loalca* 1.2—4 mg/kg. t.d.s. for 10 days. The course may be repeated after 3-4 weeks. (c) For *O. volvulus*, an initial dose of 0.5 mg/kg/once on the first day, twice on the second, then 1 mg/kg t.d.s. and then 2 mg/kg./t.d.s. for 21 days.

For mass treatment: the reduction of microfilariae to a subinfective level can be effected by 2 mg/kg. t.d.s. after meals for 7 days. The same dose is also used for prophylaxis against filaria infection.

Toxicity: Headache, malaise, weakness, arthralgia, anorexia, nausea and vomiting are the common toxic manifestations. Further, due to the destruction of the microfilariae, particularly in patients with onchocercosis, there is a violent reaction well marked in 16 hrs. after the first dose, characterised by the swelling and oedema of the skin, intense itching, enlargement and tenderness of inguinal lymphnodes, fine papular rash, hyperpyrexia, tachycardia and headache. This is a *Herxheimer type* of protein reaction. The symptoms persist for 3-7 days and then subside, after which, quite high doses can be tolerated without any further reaction.

Therapeutic status: Radical cure can be achieved with the drug in infestations with *W. bancrofti*, *W. malayi* and *loalca* by a single or multiple courses of treatment. In *O. volvulus* infestation, radical cure is unlikely but control can be achieved by short, periodic courses of treatment.

Suramin: It is a urea derivative, employed to kill adult worms of *O. volvulus* but it is not effective in the treatment of other filarial infestations. It kills the female worms and microfilariae but the males are resistant to it. **Dose:** Suramin Na 10% I.V. after a trial dose of 200 mg. A dose of 1 gm. is given every week for 6-7 weeks. Its side effects are: nausea, vomiting, shock, fainting, urticaria, albuminuria, haematuria and blood dyscrasias.

The drug is used in the treatment of onchocercosis, after an initial course of treatment with diethylcarbamazine. It is toxic and has to be used with discretion, starting with smaller doses.

OTHER PARASITIC DISEASES

Schistosomiasis: This implicates the urinary bladder, liver, as well as, the intestines, depending upon the species of the parasite. It causes cystitis with polypoid growth. The symptoms range from the burning in micturition and haematuria to the abdominal pain and fever. This condition can also lead to the cirrhosis of liver.

Trivalent antimonials like tartaremetic, have been replaced by drugs of the type of *stibophen* and *sodium antimony dimercaptosuccinate*. Recently, a new drug, *lucanthone*, has been tried successfully.

Dracunculosis: or *guinea worm* infection is caused by *D. medinensis*. It is characterised by swelling over the part, in which the parasites lie. No satisfactory treatment, besides manual surgical removal of the worm, is known. *Hetrazan* and local injection of *streptomycine*, have been also tried. Secondary infections are to be prevented by keeping the ulcers clean.

Trichinosis: The infection takes place through contaminated meat. The *larvae* lodge themselves into the muscles and cause muscle pain, fever and weakness. No specific treatment of this condition is known but *corticosteroids* can be used to control some of the acute symptoms. Recently, *thiabendazole* has been tried with limited success.

Lung and Liver Flukes: *Paragonimus westermanii* and *P. hepatica* are the causative organisms, respectively, the former involving the lungs and causing irritation and cough. The *treatment* consists of a combination of *emetine* hydrochloride-1 mg/kg. for 12 days and also the *sulphonamides*. *Chloroquin* has also been successfully tried. The latter condition causes enlargement of liver, jaundice and fever. No satisfactory treatment is known. *Emetine* HCl and *chloroquin*, used over a prolonged period, offer the only hope that can be expected.

CHAPTER

45

ANTIBACTERIAL CHEMOTHERAPY

THE TWO PRINCIPAL GROUPS: (A) SULPHONAMIDES AND (B) ANTIBIOTICS. DEVELOPMENT, SCOPE AND STATUS OF SULPHONAMIDES

[The discovery of sulphonamido-chrysoidine or prontosil rubrum by Domagk in 1933 protecting mice against LD 1000 of streptococcus, ushered a new era in the erroneous concept that chemotherapy was effective only in parasitic infections. This was the starting point of antibacterial chemotherapy, the wonders of which, have neutralised the achievements of all other therapies of the past, in this field.

Chemically, the sulphonamides are the azo compounds, the important ones being sulphanilamide, sometimes still used topically, sulphadiazine, sulphamerazine, sulphacetamide, sulphasomidine, sulphaguanidine, the long acting sulphamethoxy-pyridazine or Kinex and sulphaphenazol or orisul. Some of them are readily absorbed, others poorly so, and some diffuse into the C.S.F. more readily, thus determining their utility in systemic infection, bacillary dysentery or in meningitis. The newer fields of therapeutic possibilities of special types of sulphonamides extend also as (a) diuretic, (b) antiglaucoma, (c) antiepileptic and (d) oral antidiabetic agents. They are specific drugs acting by substrate competition with PABA, which is their chemical analogue. They produce both ordinary, as well as severe toxicities: headache, nausea, allergic skin manifestations, blood dyscrasias, crystalluria and anurea. This last depends on the solubility or otherwise, of the acetylated form of sulphonamide in the urine, thus blocking the tubules.

The sulphonamides have a fairly wide spectrum of efficacy, irreplaceable by other drugs, in (a) meningococcal meningitis, (b) bacillary dysentery, (c) E. coli infection of the urinary tract, (d) trachoma, (e) lymphogranuloma, (f) cholera, (g) plague, (h) actinocycosis and (h) intestinal antiseptics. However, like all the other drugs of this series, they also produce drug resistance, besides agranulocytosis, which are their serious hazards.]

A remarkable achievement of unparalleled importance of the last 30 years in Pharmacology, is embodied in the discoveries of (a) *Sulpha drugs* and (b) *Antibiotics*.

To these main groups, if the *antitubercular* and *antileprotic* chemotherapeutic agents are added, that then constitute the most important chapter of '*Anti bacterial Chemotherapy*', as opposed to the '*Anti-parasitic chemotherapy*', already studied.

This type of simplified grouping of these wonder drugs, introduced at the advent of their discovery and after a long period of use of anti-

parasitic drugs, we know too well now, does not work. Some of the sulphonamides besides their efficacy in bacterial infections, work on viruses and so also the antibiotics. Further, penicillin, an antibiotic, as has been seen earlier, is the most specific drug for syphilis, which is due to *treponema pallidum* infection. Other antibiotics of broader spectrum and range of action, also work on viruses, rickettsia and spirochete infections. This is understandable when we consider that in the 'cellular affinity' to a drug, the morphology is destined to play a limited role only, in the overall perspective of the submolecular concepts.

SULPHONAMIDES

Historical Development: The pioneer discovery of the antisyphilitics by Ehrlich, in the earlier part of this century, led people think that chemotherapy would never work in bacterial infestations. This belief was due to the failure of Koch to cure septicaemia by I.V. injection of all the known antiseptics and disinfectants.

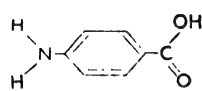
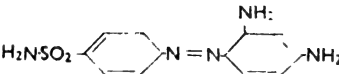
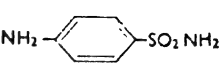
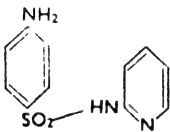
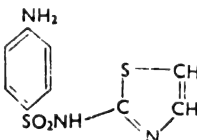
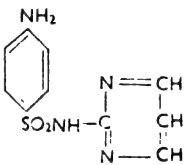
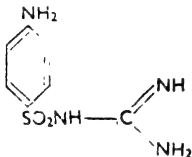
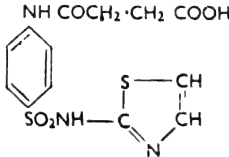
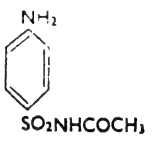
In 1933, Domagk published his challenging observations on the protective value of '*prontosil rubrum*', sulphonamido-chrysoidine, an azo compound', in streptococcal infections, protecting mice against thousand lethal doses of haemolytic streptococci. The work was soon followed in France and in 1935, Trefuel, Nitti, Bovet and Ungar, observed that a much simpler compound, the 'p-amino benzene sulphonamide' or *sulphanilamide* and not sulphonamide, which was found to be present in the urine, during 'prontosil therapy', was the active form against streptococcal infections.

The next contribution was that of the British School, where, Whitby, by introducing a 'pyridine group' in the sulphanilamide nucleus-sulpha pyridine or M. and B. (May and Baker) 693 or 'dagenan', obtained a very potent drug against *pneumo*, *gono* and *meningococcal* infections.

Though these were the important earlier stages in the discovery of sulpha drugs, many groups have since been added, with a view to decrease the toxicity, increase the polyvalency of action, induce better degrees of acetylation and solubility and also enhance their diffusion into the body fluids and C.S.F. No wonder, therefore, that over 5000 compounds have so far been synthesised and millions of pounds of sulpha drugs are being produced, all over the world, per year and the work is still continuing.

There is another aspect of this work, which is to be considered carefully. With advances in the synthesis of sulpha drugs, newer sulpho-

namides with activities other than their antibacterial chemotherapeutic actions, are being discovered. The examples of these are in the *diuretic*: diamox and *oral antidiabetic agent*-orinase, which are also sulphonamide compounds, having selective actions in noninfective conditions.

 <p>P-AMINO BENZOIC ACID</p>	 <p>PRONTOSIL</p>	 <p>SULFANTILAMIDE</p>
 <p>SULFAPYRIDINE</p>	 <p>SULFATHIAZOLE</p>	 <p>SULFADIAZINE</p>
 <p>SULFAGUANIDINE</p>	 <p>SUCCINYL SULFATHIAZOLE</p>	 <p>SULFACETAMIDE</p>

Illust. XXV. Chemical nature of important groups of sulphonamides

(a) In these compounds, the azo linkage ($-\text{N}=\text{N}-$) is unnecessary and on being split up in the body, a pharmacologically active compound with a sulphonamide group (SO_2NH_2) containing the sulphur atom, is formed. For the activity, the amino group should also be present in the para position to the sulphonamido group. If it is replaced, the activity is much lost.

(b) The sulpha drugs substituted in the sulphonamido group, with heterocyclic rings, like pyridine, pyrimidine and thiazole, as in sulpha-pyridine, sulphadiazine, and sulphathiazole, are usually more potent and less toxic. The potency of sulphonamides is related directly to their degree of ionisation and inversely to their pH. The ionised form of the compound is more potent than the undissociated molecule.

(c) In maphenide, the amino group is separated by CH_2 and therefore it is not antagonised by PABA. Succinic [$(\text{CH}_2)_2(\text{COOH})_2$] and phthalyl [$\text{C}_6\text{H}_5(\text{COOH})_2$] groups render sulphonamides unabsorbable and therefore, more suitable for intestinal infections.

Characters: All the sulpha drugs are more or less insoluble but their sodium salts are soluble and can be used parenterally.

Ordinarily, the sulpha compounds are available in powder forms and are dispensed as tablets of 0.5 gm for oral use. Their doses are variable and are to be determined according to the nature of the disease.

Preparations: *Prontosil or sulphachrysoidine:* The first to be discovered and is therefore of considerable historical importance. It has been used in purerperal sepsis and erysipelas but because of the toxicity, it has been completely discarded now.

Sulphanilamide: Chemically the simplest but now of historical importance mostly. It is less potent but more toxic than the newer compounds. It is still used *topically* in combination with sulphathiazole and proflavin sulphate, sometimes.

Sulphapyridine: It is not much used for systemic actions these days, as it is irregularly and poorly absorbed from the G.I. tract, a higher percentage is acetylated in the body and is slowly excreted. It is suitable for the treatment of certain skin diseases like dermatitis herpetiformis and lymphogranuloma.

Sulphadiazine: It is a very important compound. It is slowly absorbed from the gastrointestinal tract but the absorption is complete. It is not freely soluble in the body fluids and for preventing crystallisation, high fluid intake is to be maintained. It diffuses freely into the C.S.F. and is of great value in the treatment of meningococcal meningitis. The action is slow and prolonged and there is negligible toxicity.

Sulphamerazine: It is rapidly absorbed and slowly excreted, and its action is prolonged. It is valuable as a *prophylactic* against sore throat and rheumatic fever with one dose/12 hrs.

Sulphacetamide: It is less toxic, more soluble and is useful in *urinary tract* infections. It penetrates into the skin and the conjunctiva more readily than others and is non-irritant. It is used in *ophthalmology* in the form of an ointment 0.1 gm/ml. or solution 0.3 gm/ml.

Sulphadimidine or sulphamezathine: It is one of the best sulphonamides available. It is readily and completely absorbed from the G. I. tract. The maximum blood concentration is reached within 4 hours and maintained. Because of its solubility in acid urine, the risk of crystallisation is minimised. It is of special value for the treatment of pneumococcal infections. Toxic effects are comparatively rare.

Sulphasomidine or Elkosin: It is soluble and readily absorbable and diffusable into the body fluids. It is slightly acetylated and rapidly excreted from the body. It provides high blood levels in moderately low doses and is frequently employed in *urinary tract infections*, suscep-

tible to sulphonamides. *Gantrisine* is also used in urinary tract infections.

Triple sulphas: This was designed to minimise the renal toxicity, without affecting the therapeutic effectivity. There are two such combinations:

- (a) Sulphadiazine + sulphamerazine + sulphamethazine) or
- (b) Sulphadiazine + sulphamerazine + sulphacetamide) — all in equal quantities.

Sulphafurazole: It is more soluble in *acid urine* and consequently, there is less risk of crystal formation and crystalurea.

Sulphasomizole: It is a moderately long acting sulphonamide and is much less toxic. The effective concentration can be maintained by giving doses at 12 hours interval. There is also less risk of crystalurea.

Sulphaethylthiadiazole: a medium acting sulphonamide compound and is given at 8 hourly intervals. Further, because of its solubility in acid urine, its renal toxicity is negligible.

Maphenide or marphanil: A locally active compound which is effective even in the presence of *pus* and also against sulphonamide-resistant organisms. At times, it is used in combination with sulphonamides and antibiotics. Its antibacterial actions are not antagonised by PABA.

Sulphasalazine: It is a combination of 5-aminosalicylic acid and sulphapyridine and is used in bacterial infections, associated with ulcerative colitis.

Sulphaguanidine: A *locally acting* sulphonamide, with restricted systemic absorption and toxicity. The high intestinal concentration makes it efficacious for bacillary dysentery, cholera and for the sterilization of gut.

Phthalyl-sulphathiazole: or *Thalazole*, is also a poorly and slowly absorbed sulphonamide. In the intestine, free sulphathiazole, which is the active form, is liberated. Its uses are the same as of sulphaguanidine, and more particularly, as a prophylactic in abdominal surgery for resection of colon. Its special advantages are—smaller dosage-schedule and effectivity, in patients with watery diarrhoea.

Succinyl sulphathiazole: Another member of the same group, the drug is hydrolyzed by the intestinal flora to sulphathiazole, to produce its bacteriostatic action, which it resembles in actions and uses, though somewhat less potent. It can occasionally give rise to skin rashes, mild anaemia, fever and polyneuritis, for which, vitamin supplement, is needed.

Sulphamethoxypyridazine: (*Kynex*). It is a long acting, *one-dose* sulphonamide maintaining adequate blood concentration for 12-24

hours, in a dose of 1-2 gm/day. It is readily absorbed but slowly excreted, with likely cumulative effect, particularly in renal impairment. It is used as a *prophylactic*, while for acute conditions, sulphadiazine is preferred. Most of these drugs get bound in plasma protein and only a small quantity is in *free-form*. About 15% is acetylated and 25% excreted in first 24 hours, in urine. An optimal level of fluid intake, with a daily urinary output of one litre, should be ensured.

Sulphadimethoxypyridazine (Madribon): possessing virtually the same properties as Kynex, it is rapidly absorbed, slowly excreted and has a prolonged action. It is used in G.I., urinary and respiratory tract infections and also in skin conditions. The untoward effects, though infrequent, have been reported to be—abdominal pain, G.I. upset, generalised urticaria and eosinophilia, which are not of much serious consequences.

Sulphaphenazol (Orisul): is one of the latest in the series, its actions and plasma concentrations being intermediate between sulphadiazine and Kynex. It is soluble in acidic urine and crystalluria is much less frequent. Amongst the long acting sulphonamides, in view of quicker, less cumulative and less toxic effects, it is probably the most widely used for upper respiratory and urinary tract infections and in oral surgery and extraction of tooth.

This long list, even of selected preparations, present several points, at a glance, for consideration, in respect of their *merits* and *demerits*. The first 3 compounds, incidentally also the earliest in the sequences of discovery, are almost out of use now, because of their irregular metabolism and toxicity. *Sulphadiazine*, *triple sulpha*, and *sulphasomidine* have better diffusion in body fluids, solubility and absorbability. *Sulphacetamide* and *marfamil* show better penetration into skin and m.m. The *guanidine-thiazol* group has less systemic absorption, higher intestinal concentration and more local action on the gut. *Lastly* the *long acting*-kinex, madribone and orisul, have the advantages of 1 or 2 doses per day for induction and maintenance of optimal blood concentration. However their *drawbacks* are—(i) gradually rising blood level, higher degree of protein binding, longer fixation, risk of untoward interaction, and also variable degrees of acetylation (ii) Slow excretion lasting for one week, making them unsuitable for acute infections and (iii) unsatisfactory penetration into the C.S.F. *Special points* also are—(a) poorly absorbed group acting in gut infections and sterilisations (b) Marphanil acting in the presence of PABA (c) Salazine in ulcerative colitis and (d) Orisul and sulphamerazine as sore throat and ARF prophylactic.

Classification: This is fairly complex, because of large number of approaches, besides the chemical one, already presented. The issue has to be considered under different parameters, each one of which, has its own importance. Some of the accepted ones are—(a) *Duration of action*—short or long acting, (b) *Intestinal absorbability*—regular,

irregular, slow and rapid, (c) *Locus of action*—systemic, local, topical, (d) *Plasma concentration*—high or low, rapid or slow and nature of protein binding (e) *Diffusion in body fluids* and C.S.F.—slow or rapid; adequate or inadequate, (f) *Degree of acetylation* and solubility in acid or alkaline urine and, also (g) *Nature of activity* and toxicity etc.

RAPIDLY ABSORBED AND EXCRETED	Sulphadiazine, Sulphamerazine, Sulphamethazine, Sulphasomidine.
RAPIDLY ABSORBED AND SLOWLY EXCRETED	Sulphamethoxypyridazine, Sulphadimethoxypyridazine.
POORLY ABSORBED	Succinylsulphathiazole, Phthalylsulphathiazole, Sulphaguanidine, Phthalylsulphacetamide and Paranitrosulphathiazole.
DIFFUSED IN CSF & BODY FLUIDS	Sulphadiazine, Triple sulpha, Sulphamerazine and Sulphamethazine.
LONG ACTING	Sulphamethoxypyridazine (Kynex) Sulphadimethoxypyridazine (Madrison), Sulphaphenazole (Orisul).
HIGHLY ACETYLATED	Sulphapyridine, Sulphasuxidine, Sulphapyrazine.
TOPICALLY ACTIVE	Sulphacetamide, Marfanil.

Metabolism: *Absorption* takes place from the small and large intestine, the degree and the speed, varying with different preparations. *Water solubility* does not determine the rate of absorption e.g. sulphadiazine though insoluble, is easily absorbed, while, sulphathaladine is water soluble and yet not readily absorbed. Soda. bicarb helps in the absorption of sulphonamides, to some extent only.

Distribution: This is fairly uniform in most of the tissues with the exception of brain. The sulphonamides pass into the transudates and exudates and also into placental circulation, but only sulphadiazine and sulphamerazine diffuse into the C.S.F., more readily, in meningitis. As proteins in C.S.F. increase in meningitis, the quantity of sulphonamide bound to the proteins, rises and an adequate blood concentration is reached in 3-4 hours.

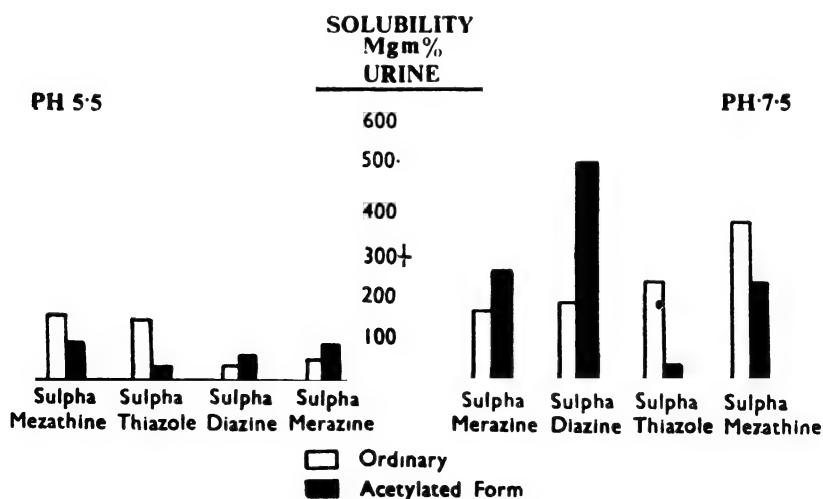
Fate: The sulphonamides are present in the blood in 3 forms—(a) partly in free state, (b) partly bound to the plasma proteins, and (c) partly acetylated. Only the first form is therapeutically effective. The binding capacity of different sulphonamides with plasma proteins varies and it acts as a depot tending to prevent any abrupt changes.

However, the greater the combination with proteins, the lesser is the tissue diffusion and concentrations.

Acetylation: The sulphonamides are acetylated in the *liver* and the acetylated form is therapeutically ineffective, toxic but rapidly excreted. There are wide individual differences in the degrees of the acetylation.

Drug	Acetylation %	
	Blood	Urine
Sulphadiazine	15	30
Sulphamerazine	15	45
Sulphanilamide	15	40
Sulphathiazole	20	20
Sulphaguanidine	25	25
Sulphapyridine	30	70
Succinyl sulphathiazole	50	55
Sulphapyridine	65	70

If the acetylation is more and the solubility is less, in urine, *crystalluria* and renal concentrations may occur. The acetylated form is more soluble in alkaline urine and hence administration of sodium bicarbonate (4-12 gm/day) and increased water intake, prevent these side-effects.



Illus : XXVI Relative solubility of ordinary and acetylated form of sulphonamides in urine

Excretion: (a) About 90-98% of the absorbed sulphonamide is excreted in urine, in 2-3 days, the renal mechanism of clearance being practically the same as of urea. About 60% of the filtered sulphonamide is again reabsorbed by the tubules. (b) The rate of clearance of the conjugated form of sulphonamide is greater and fluid intake further facilitates its clearance. The urinary concentration of sulphonamides is about 10 times greater, which enhances its effectiveness in urinary infections, permitting even bactericidal action, in most of the cases.

Optimal blood concentration: (i) Severe infection: 10-15 mg. %
 (ii) Moderate infection: 7-10 mg. %
 (iii) Mild infection: 4-7 mg. %

The sulphonamides can be estimated in the blood, urine and the tissues by the *Method of Bratton and Marshall*. This is a colorimetric test, based on the principle of diazotisation.

DOSE AND BLOOD CONCENTRATIONS

Patients Wt. in Kg.	10-15 mg. %			4-8 mg. %		
	Initial Dose gm.	Maintenance Dose/4 hr. gm.	Dose in 1st 24 hr-gm	Total Dose 24 hr	Daily Dose gm,	Dose/ 4 hr.
70	4.8	1.2	0.15	10.5	5.4	0.9
45	3.6	0.9	0.18	8.1	5.4	0.9
11	1.8	0.3	0.3	3.3	1.8	0.3

Mode of Action: Though not yet absolutely established, the following indicates the approximate position:

(a) The sulpha drugs do not neutralise bacterial toxins *in vitro* but 'S' containing substances inactivate endotoxins. They do not stimulate the production of antibodies and consequently, do not induce any immunity reaction in the body.

(b) Sulpha drugs are capable of producing metabolic and morphological changes in the germs and the presence of fever reactions associated with the infection, enhances sulphonamide activities.

(c) The sulphonamide have definite antibacterial properties, in the form of bacteriostatic and/or bacteriocidal actions, depending upon the concentration of the drug in the tissues. In the former action, both the granulocytes, as well as the reticuloendothelial system, also play their roles in effecting bacteriostasis.

(d) Changes in the chemical nature of the compounds alter their physico-chemical properties of solubility and degree of ionisation, which seems to be responsible for the selective action of these drugs, in infective conditions.

Theory of Woods and Fildes: In 1940, these workers observed a reciprocal relationship between para-aminobenzoic acid (PABA) and the sulphonamides.

P-aminobenzoic acid is an important metabolite of microorganisms and is the chemical analogue of sulphonamides. It possesses antisulphonamide activity *in vitro*, as observed during the process of suppuration. Those germs which produce excesses of PABA, are resistant to the sulphonamide therapy.

Sulpha drugs and PABA appear to compete with each other for the bacterial enzyme receptors, which are responsible for the biosynthesis of folic acid, an essential metabolite for sulphonamide sensitive organisms. It seems likely that sulphonamides by inhibiting the utilisation of PABA, prevent cellular synthesis of folic acid and thus disturb its growth and multiplication. This is due to the structural similarity of sulphonamides and PABA and the germs cannot discriminate between the two analogues, thus depriving them of their essential metabolite. In this case, the inhibition is *competitive* in nature, as even a small quantity of PABA is capable of overwhelming the effect of a large concentrations of sulpha drugs. This is thus an example of *competitive antagonism*. Other substances capable of antagonising the actions of the sulphonamides include methionine, folic acid, some purines, pyrimidines and peptone. Recently, *glucoreductone* has also been found to be one of the essential metabolites and the sulphonamides may prevent its utilisation by forming a stable compound.

Resistance Formation: This is a real hazard associated with the use of specific drugs, working mostly through the enzyme systems. Haphazard and indiscriminate use of potent drugs at suboptimal concentrations or for unnecessarily long periods in cases of rapidly multiplying organisms, enhances this hazard, while their correct uses with adequate doses, so as to maintain the effective plasma concentration in cases of sensitive organisms minimise this paradox.

The underlying mechanism involved in resistance formation, may be in the synthesis of essential metabolites, development of alternative metabolic pathways for the synthesis, or utilisation of drugs as metabolites, by variations in the enzyme adaptation and production of mutant forms, carrying the resistance through successive generations,

known as '*variation by selection*', are some of the hypotheses. This has been fully discussed in the *Chapter of Antitubercular Drugs*.

Routes of Administration: (a) *Oral*: It is the route of choice. The rate of absorption is as good as by any other route. It also permits the maintenance of a sustained level of drug concentration in the plasma and tissues and is easy, cheap and fully satisfactory.

(b) *Parenteral*: The soluble sodium salts of sulphadiazine, sulphamerazine and sulphadimidine are used by I.M. or slow I.V. injection, as 5% solution; in comatose conditions only, otherwise the oral route is adequately satisfactory.

(c) *Intrathecal*: This is often unnecessary and the sodium salts are contraindicated for this.

(d) *Topical*: Used for the skin and the dressing of wounds. The risk of sulphonamide resistance and *sensitivity reactions*, are to be borne in mind.

Toxicity: This occurs from idiosyncrasy, drug sensitivity and toxic doses. About 10% of the patients do not tolerate sulpha drugs and produce *mild, moderate or severe* toxic manifestations, as detailed below:

Mild: Headache, nausea, dizziness, mental depression, are the mild conditions, occurring in many cases.

Moderate: Skin manifestations, drug fever, cyanosis and peripheral neuritis, which are *moderately severe* conditions, may also occur in some percentages of cases. Rashes, erythema nodosum and exfoliative dermatitis, a type of sensitisation reaction, and even photo-sensitisation of the skin and cornea from sulphathiazole and sulphapyridine, also occur. Drug fever also is a sensitivity reaction. Cyanosis though quite rare, occurs from sulphaemoglobin and meth-haemoglobin formation. Peripheral neuritis may be due to vitamin B₁ deficiency from disturbances in its biosynthesis in the intestine.

Severe reactions: (a) *Blood dyscrasis*—Leucopenia, Agranulocytosis and Haemolytic anaemia. These usually occur after 4 weeks of treatment and regular T & D. and Hb. examination are necessary. Its treatment comprises stopping of the drug, administration of fluids, alkalis, vitamin B complex, haematinics and pentnucleotide.

(b) *Crystalluria, haematuria and anuria*: They occur more frequently from sulpha pyridine and sulphamerazine. The solubility or otherwise, of the acetylated forms of sulpha drugs in the urine, at a particular pH, is responsible for this.

In any prolonged therapy, therefore, such reasonable precautions as: (a) bed rest, (b) increased fluid intake, (c) sodium bicarbonate and sodium citrate 1 gm. each (d) avoidance of purgatives and no medication beyond one week, (e) sulpha combinations and lastly, (f) a watch for early toxic manifestations, are advisable.

ANTIBACTERIAL SPECTRUM

<i>Micro-organisms</i>	<i>Sensitivity (M.E.C.) %</i>
Meningo, pneumo and streptococcus haemolyticus: Shiga and flexner bacilli.	0.1-1 mg.
E. Coli. gonococcus, friedlander's and influenza bacilli	1-3 mg.
B. pestis, anthracis, v. cholerae and trachoma virus	3-10 mg.
B. proteus, staphylococcus aureus, Cl. welchii, actinomyces and brucella.	10-30 mg.

THERAPEUTIC CONSIDERATIONS

The sulpha drugs act on a very wide range of microorganisms: (a) some of the *cocci* and *bacilli*, (b) the gram positive and negative organisms, (c) the capsulated and non-capsulated, (d) also some of the aerobic, as well as anaerobic organisms. They do not however act on viruses, excepting that of trachoma, spirochetes, protozoas, B. typhosus and common cold organisms.

For *rational use*: (a) accurate diagnosis, (b) selection of suitable compounds, (c) maintenance of optimum concentration—by adhering to initial, maintenance and spacing of doses, (d) suitable fluid level (2-3 lits/day) and (e) alkalinisation with sodi bicarb 2-3 gms, (f) gradual reduction of dose and (g) a careful watch on the toxic symptoms, as and when they appear, is necessary. The following are some of the established uses of the sulphonamides:

Meningococcal Meningitis: It is unrivalled both for prophylaxis as well as, treatment of this condition.

- (a) *Sulphadiazine* and *sulphamerazine* are preferred, because of their diffusion in C.S.F., making intrathecal medication often unnecessary. An initial dose of 4 gm, 1 gm/4 hr is recommended.
- (b) If the patient is unconscious, 5 gm of sulphadiazine I.V. in 100 ml of saline and then 1 gm/4 hourly, till the patient returns to normal

and the C.S.F. culture is negative. Marked improvement is usually noticed in 24-48 hours.

- (c) For *prophylaxis*, 2-3 gm/day, for 2-3 days, brings down the *carrier-rate* to zero. With the above therapy, the mortality rate has been reduced from 90% to 20%, approximately.

Bacillary Dysentery: *Sulphagunidine*, *sulphathalidine* and *sulphathiazine* 2-4 gm., initially and then 2 gm. every 4-6 hrs., is the treatment-schedule of choice, in all acute cases. *Streptomycin* $\frac{1}{2}$ —1 gm/OS/4 times a day, may also be used. In cases of any prolonged use, vitamin B. complex and vitamin K. supplements, are essential.

Pneumonia: Sulphadiazine and sulphamerazine are the drugs of choice, in pneumococcal meningitis, peritonitis and endocarditis and pneumonia. By this therapy, the mortality rate has been reduced from 27% to 4% but penicillin has reduced it further to 0.7% only and is the drug of choice now, in all cases of pneumococcal pneumonia.

E. Coli Infection: (a) Sulphonamides are of value in the treatment of urinary infections. Sulphadiazine, sulphamerazine and sulphamethazine all have been used. *Elkosin* which has the advantage of limited acetylation and free from greater solubility in acid urine, is now preferred. (c) Triple sulphas and gantrisin are also sometimes used. *Dose:* 1 gm./4 times/day.

Trachoma: Sulphadiazine systemically, as in other infections and sodium *sulfacetamide* 30% solution, locally, once per day, or 6% ointment twice daily, constitute a satisfactory form of treatment for this viral infection.

Herpetiform Dermatitis: It responds to *sulphapyridine*: 0.5 to 1 gm. t.d.s.

Lymphogranuloma: This also responds well to the sulphadiazine therapy. Initially, 4 gm., followed by 1 gm. every 4-6 hours, may be used.

Cholera: It responds better to sulphonamides than antibiotics. *Sulphadiazine*—6 gm. initially, followed by 1 gm./every 6 hours. *Streptomycin* and tetracyclines may also be tried. With this, as well as, *adjuvant saline therapy*, the mortality rate has been reduced from 30% to 7% only.

Plague: With sulphadiazine, in combination with streptomycin, the mortality rate has now been reduced to 4% only, as compared to 90%

in the untreated cases. *Dose*: A blood concentration of 10-20 mg% is needed. Streptomycin is withdrawn on the 5th day and sulphadiazine withdrawn on the 12th day.

Actinomycosis: Sulphomides and Penicillin are the effective agents, some strains being sensitive to sulphonamides and others to the use of penicillin. The combined therapy gives better results.

Organisms responding *predilectively* to sulphonamides and not to penicillin are: (a) the colon—dysentery group, (b) Friedlander's pneumo bacillus (c) Ducrey's bacillus and (d) Klebsiella Lymphogranulomas. Their uses, in spite of antibiotics, thus remain unaffected, in: (a) Bacillary dysentery (b) Meningococcal meningitis (c) Acute urinary tract infections (d) Cholera (e) Plague (f) Trachoma (g) Lymphogranuloma and lastly (h) Preoperative intestinal antisepsis.

Regarding the *sulphonamide combinations*, it is argued that this offers better absorption, peak higher levels, less nephrotoxicity and less hypersensitivity reactions. It also permits the attacking of the organisms at different strategic points. These concepts have not been fully substantiated by clinical experience. As in the case of cholroform and ether mixture, sulphonamide combinations, whatever may be their theoretical merits, are less often used than the individual drugs. Further, in all such cases of drug combination, the increasing hazards of drug interaction, has also to be kept in view, till controlled and continued assessments, prove otherwise.

Plate XXXVIII
SOME COMMON BACTERIA



Fig. 102. Gram : Staph and Streptococci



Fig. 103. *D. Pneumoniae*

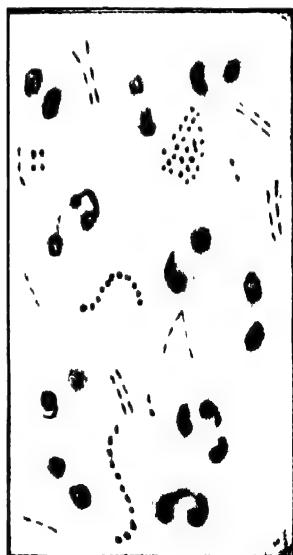


Fig. 104. *M. Tuberculosis* (Acid Fast)

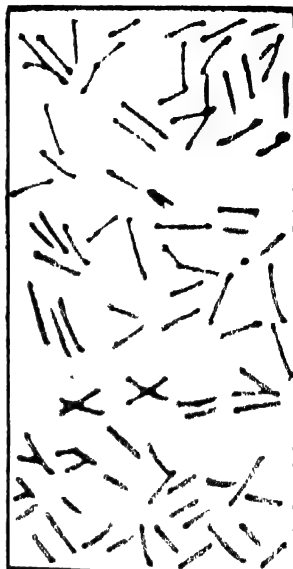


Fig. 105. *C. Diphtheriae*

CHAPTER

46

PHARMACOLOGY OF ANTIBIOTICS

GENERAL CONSIDERATIONS: DEFINITION. SOURCE AND CLASSIFICATION. MODE AND SPECTRUM OF ACTION. SPECIAL FEATURES AND SCOPE OF USE

[The antibiotics which have been obtained from moulds and soil bacteria, in recent decades, shortly after the discovery of sulphonamides, have proved to be even a greater triumph over microbial infections, with a more expanded horizon. Conventionally, they are classified as—(a) *Narrow spectrum*: Penicillin and streptomycin, (b) *Broad spectrum*: Chloramphenicol and tetracyclines (c) *Newer antibiotics*: Erythromycin, cycloserine and polymixins. Alternatively, they can also be classified as (a) *Antibacterial* (b) *Antitubercular*, (b) *Antiviral*, (d) *Antirickettsial*, (e) *Antimycotic* and (f) *Antimalignancy antibiotics*. Most of them act specifically, by biochemical, metabolic mechanisms and induce drug resistance.

Penicillin finds its unrivalled uses in (a) Syphilis (b) Pneumococcal pneumonia, (c) Coccal infections and (d) Surgical prophylaxis. *Streptomycin*—which is toxic for the 8th nerve and produces worst resistance, is used in (a) *Tuberculosis* (b) Urinary tract infection (c) Intestinal infections (d) Brucellosis, granuloma and also plague infections. *Chloramphenicol* finds its use in (a) Typhoid fever and along with tetracyclines, also in (b) Rickettsial and (c) Viral infections and (d) Meningitis from H influenza etc.

Their continued use may cause *intestinal moniliasis* and vitamin B deficiencies. The newer antibiotics possess similar spectrum of activities, as above, but are used as *second line* drugs, when others fail. The *antifungal antibiotics*: mycostatin, amphotericin and griseofulvin are used in intestinal moniliasis and the last also in superficial and deep seated fungal infections of the skin.]

General Considerations: This is a young and virile group of drugs which act specifically in infective conditions, and has revolutionised modern therapeutics to a measure, not dreamt of in the past.

As stated in the introduction, it was observed that certain organisms created favourable circumstances for the existence and growth of others, while others, showed antagonistic reactions to other types of living organisms, as, in the observation of Pasteur, some air-borne bacillus was capable of inhibiting the growth of anthrax bacilli, in his culture media.

If the association of micro-organisms exerts a mutually favourable influence on each other, the action is termed as *symbiosis* and if it

is unfavourable, the action is known as *antibiosis*. This was the original concept of antibiotics leading towards their discovery.

An antibiotic is defined as a chemical substance, derived from living organisms and having an inhibitory or lethal action, on micro organism, in low dilutions, in a specific manner. If the drugs possess similar actions but are of chemical and synthetic origin, they are called *chemotherapeutic drugs*. In this context, there is a reciprocal relation between the two groups and an antibiotic after successful synthesis, could become a chemotherapeutic drug, in due course, indicated earlier.

After the discovery of 'penicillin' from a common mould, *Penicillium notatum*, an intensive search for antibiotic producing organism, in nature, was made and a large number of sources for obtaining clinically effective antibiotics discovered. They comprise mostly the actinomycetes and fungi, indicated below. The fungi of medicinal importance, besides being important sources for antibiotics, are several. The representative ones are shown in *Plate XXXIX* Fig. 106.

<i>Organisms</i>		<i>Antibiotics</i>
<i>Penicillium notatum</i>		Penicillin
<i>Penicillium griseofulvum</i>		Griseofulvin
<i>Aspergillus fumigatus</i>		Fumagiallin
<i>Streptomyces</i>	<i>grisus</i>	Streptomycin
"	<i>venezuelae</i>	Chloramphenicol
"	<i>aureofaciens</i>	Chlortetracycline
"	<i>rimosus</i>	Oxytetracycline
"	<i>erythreus</i>	Erythromycin
"	<i>vinacacious</i>	Viomycin
"	<i>faradiae</i>	Neomycin
"	<i>kanamyceticus</i>	Kanamycin
"	<i>halstedii</i>	Carbomycin
"	<i>nodosus</i>	Amphotericin B
"	<i>nouresae</i>	Nystatin
"	<i>antibioticus</i>	Oleandomycin
"	<i>caryophylus</i>	Cycloserine
<i>Bacillus licheniformis</i>		Bacitracin
<i>Bacillus polymyxa</i>		Polymyxin
<i>Bacillus brevis</i>		Tyrothricin
SEMI SYNTHETIC		Tetracycline, dihydrostreptomycin, Methicillin, ampicillin.

The quality, quantity and type of antibiotics can be controlled by using genetic techniques, artificial mutation and selective biosynthesis.

Plate XXXIX

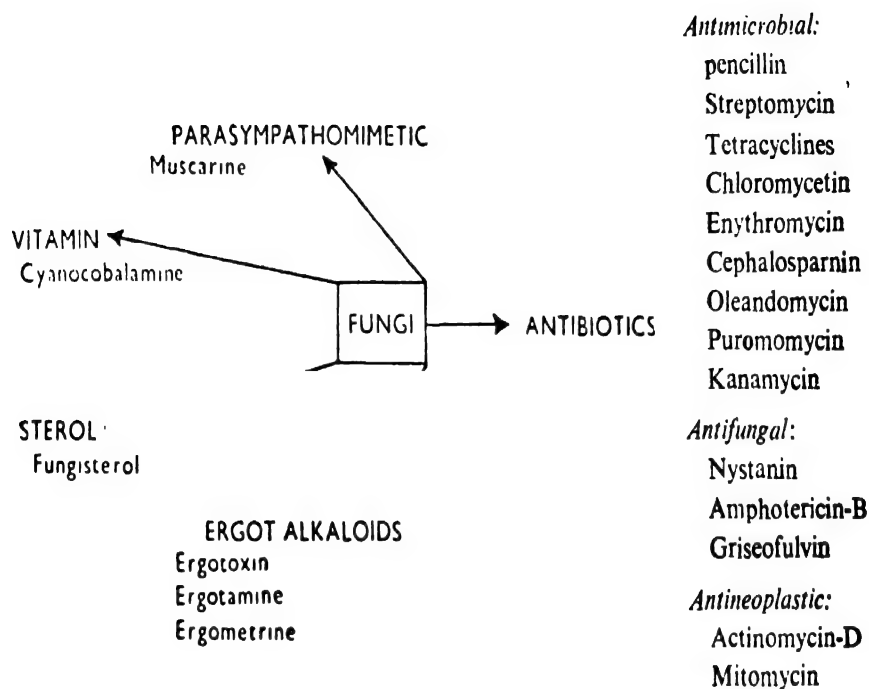


FIG. 106 Fungal drugs of importance

Trillions of units and millions of pounds of antibiotics are being manufactured every year and a dozen of newer ones are being discovered during the same period. The work so far carried out, has offered many newer concepts of drug action, at biochemical and cellular levels and ceaseless search is still going for the discovery of better and more ideal antibiotics for therapeutic uses.

Classification: This is usually based on the range of different types of organisms on which an antibiotic acts, thus denoting its *spectrum of activity*, as well as, from its mode and scope of uses.

NARROW SPECTRUM ANTIBIOTICS	Penicillin, streptomycin
BROAD SPECTRUM	Chloramphenicol, tetracyclines
NEWER ANTIBIOTICS	Erythromycin, cycloserin, novobiocin, oleandomycin.
TOPICALLY EFFECTIVE ANTIBIOTICS	Bacitracin, polymyxin B, neomycin.
ANTIAMOEBIIC ANTIBIOTICS	Fumagillin, puromycin, tetracycline.
ANTIFUNGAL ANTIBIOTICS	Griseofulvin, nystatin, amphotericin B.
ANTIMALIGNANCY ANTIBIOTICS	Puromycin, mitomycin C. actinomycin.

These groupings are still somewhat arbitrary. The narrow spectrum antibiotics possess intensity of action and are also more prone to provoke resistance formation. The broad spectrum antibiotics act also on rickettsia and viruses, besides bacteria, but their action somewhat lacks the intensity of penicillin. The newer antibiotics possess effectiveness in limited fields and the antifungal and antimalignancy groups act on certain specialised organisms and cells, respectively.

An Ideal Antibiotic: which is more imaginary than real, should have some of the following essential pre-requisites:

(a) Wide range of activity minimising diagnostic hazards. (b) Minimum toxicity, high therapeutic index and absence of resistance formation. (c) Bactericidal rather than bacteriostatic action (d) Nodeliterious action on intestinal flora, disturbing vitamin biosynthesis, (e) No allergic reaction. (f) Ease of diffusion in body fluids by crossing blood-tissues and bloodbrain-barriers. (g) Stability of solution at room temperature, satisfactory dosage form and ease of absorption from all routes of administration (h) Easy attainment and maintenance of optimal tissue concentration for prolonged action. (i) Synergistic actions with other antibiotic and/or chemotherapeutic agents. (j) Low cost and no need for having any elegant dosage-forms. These obvious-

ly are too high ideals for achievement and none of the antibiotics, at present, fulfil the objectives, excepting probably penicillin and tetracyclines, which approach these goals to some extent only.

Mode of Action: This is complex and understood in parts only:

1. The antibiotics may act as bacteriostatic or bacteriocidal, depending on the concentration used. Their modes of action vary according to organisms and their degrees of sensitivity. As a rule, young cultures and rapidly multiplying organisms are more susceptible to their actions, with certain provisos. Unlike sulphonamides, they act in the presence of pus, blood, serum and organic matters.
2. Inhibition of synthesis of mucopeptides of bacterial cell-wall, leading to its lysis, is produced by penicillin, bacitracin, cycloserine, and vancomycin. Similarly, the cell-membrane which is concerned with the synthesis of metabolites, through a battery of enzymes, is disturbed by polymyxin, novobiocin, tyrothricin, nystatin and amphotericin, which accounts for some of their actions.
3. Ribonucleic acid plays a vital role in nucleic acid synthesis and its turnover is increased in rapidly multiplying organisms, more specially in the cell-wall of the gram positive organisms. This is inhibited by penicillin, explaining the sensitivity of these organisms to penicillin therapy. Penicillin also inhibits the SH group of enzymes, which is needed for RNA synthesis for maintaining the integrity of bacterial cell-wall. This is accepted as another plausible explanation for penicillin action.
4. A number of antibiotics, more particularly chloramphenicol and also streptomycin, tetracyclines, erythromycin, and neomycin, inhibit protein synthesis, preventing the utilisation of aminoacids in the formation of peptide bonds. This has been assigned, partly to the antibacterial action of some of these antibiotics. Chloromycetin is believed to interfere this synthesis at the stage of tryptophane incorporation. As this is partially inactivated in cases of viruses and rickettsias, resistance formation, in these organisms, is minimal.
5. Some of the antibiotics like chloramphenicol are known for their antimetabolite action, preventing the utilisation of aminoacid, *phenyl alanine*, thus disturbing the cellular biochemical activity, related to their growth and multiplication.
6. Besides the above, other factors like *chelation of cations*, binding

of Ca, Mg, Mn, and also inhibition of *oxidative phosphorylation* in the mitochondria, have been implicated in the mechanism of action of tetracyclines.

Resistance Formation: The development of resistance of an organism to any antibiotic is an important therapeutic problem. Though some organism have a natural resistance to certain antibiotics, acquired resistance to the continued use of a drug by a sensitive organism, is more important. For this, *sensitivity test* of a given organism vis-a-vis any particular drug, indicated for use, has always to be determined before starting the use of an antibiotic. For this, bacterial sensitivity test, by following the 'cup-plate' method, detailed under penicillin assay, against the organism, for which, a given antibiotic is proposed to be used, is to be carried out for eliciting the bacterial sensitivity to the drug, almost as a routine manner, in view of increasing incidences of drug resistance, in these days.

NARROW SPECTRUM ANTIBIOTICS

They comprise *two* most important antibiotics: (a) *Penicillin* and (b) *Streptomycin*, both of which, are *life saving* and unchallenged specifics, for a number of conditions, not necessarily limited to one or two groups of organisms only.

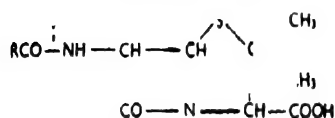
PENICILLIN

Historical: In 1877, Pasteur casually observed the bacteriostatic effect of certain organisms against others. In 1929, Alexander Fleming, while culturing *staphylococcus aureus*, observed spontaneous lysis of certain colonies by moulds, later isolated as *Penicillium notatum*, yielding penicillin, as active principle. The discovery passed unnoticed before the rising glory of the *sulpha drugs* till Chain and Florey, undertook systematic studies of penicillin, in 1940, on experimental basis and from that time onward, penicillin gradually established its rightful position, as a specific for all the diseases, for which, it is used in different preparations and dosage-forms.

Chemistry: Penicillin is a metabolic product of *P. notatum* and *P. chrysogenum*, common types of fungi abounding everywhere and growing in ordinary *soya bean* or *corn steep liquor*, a waste product of corn starch, in 7-10 days, at room temperature. The washings are extracted with different solvents, purified and crystallised. The *yield*

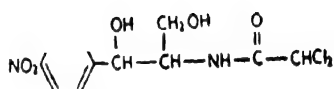
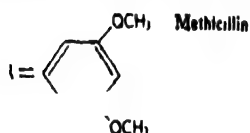
Plate XL

6' Aminopenicillanic acid



R = C₆H₅.CH₃ = Penicillin G.

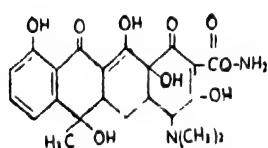
R = C₆H₅.OCH₃ = Penicillin V.



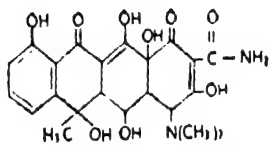
CHLORAMPHENICOL

FIG. 107 Structure of penicillin

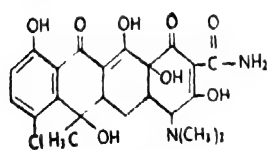
FIG. 108 Chloramphenicol



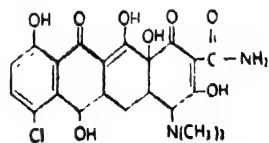
TETRACYCLINE



OXYTETRACYCLINE



CHLORTETRACYCLINE



DEMETHYLCHLORTETRACYCLINE

FIG. 109 Tetracyclines

is usually low—1 gm/100 gallons. It has now been increased thousand fold by special devices of enriching the medium with amino acids—tryptophan, alanine, aeration and also by enriching *P. chrysogenum* by irradiation. This has also permitted the isolation of different isomers of Penicillin G. K, X, F and dihydro-F. The culture can now be altered as desired, to increase or decrease any of these forms.

Biosynthetic penicillin: Vicillin and Benzyl penicillin are obtained by modifying the culture medium with different precursors, referred above.

Chemically, penicillins are *B-lactum thiazolidine derivatives* possessing dipeptide structures. *Penicillin G* or benzyl-penicillin, is the simplest derivative and most commonly used. Phenoxymethyl penicillin or *penicillin V* and *methicillin*, are also closely related. The basic structure of different forms of penicillin, are shown in *Plate XL*; Fig. 107. Penicillin G has an *empirical formula* of $C_{14}H_{18}NO_6$ and possesses alanine and cystine dimethyl rings. The dry powder is comparatively stable but may undergo hydrolysis by penicillin-lactamase (penicillinase), metal ions and alkalis. The sodium and potassium salts, which are crystalline, are much more stable than the amorphous form and are therefore used in therapeutics.

Types of Penicillin: There are many, some of which, like, Penicillin G and its derivatives—procaine penicillin, benzathine penicillin, penicillin V and diethylaminoethylester, represent the older group, while methicillin, phenethicillin, cephalopirin, are the *newer members*.

Penicillin G—This is the commonest form and is used as injection, ear and eye drops and sometimes in oral dosage-forms, in each of which case, high blood level is not easily attained and the intestinal flora are also disturbed.

Procaine Penicillin G—Introduced in 1948, for prolongation of action. It is a combination of penicillin and procaine and is also available in the form of suspension in oil, with aluminium stearate, known as PAM. Procaine-penicillin causes sensitisation reaction, more frequently than the crystalline form.

Benzathine Penicillin—A long acting *repository form* of penicillin G, a single I.M. injection, maintaining blood concentration upto 7 days. It is also absorbed by the oral route and it can therefore be given by mouth.

Phenoxymethyl Penicillin or Penicillin V: It is also suitable for oral administration, as it is not affected by gastric acidity. It maintains a fairly high blood concentration. It is given in doses of 3 lacs units/tds/orally, in *mild infections* only.

Penicillin G diethylaminoethylester: It is an insoluble depot preparation, concentrating more in the lungs and C.S.F. It is used as a suspension but the action is not very prolonged.

Compcicillin—or Hydrabamine Penicillin G—Containing ethylene diamine: *Dose*—3.5 lac units/6 hr/O.S.

Vicillin K (Penicillin V Potassium)—It is the potassium salt of penicillin V and is very quickly absorbed from the upper part of the small intestine. It produces faster and higher blood levels than the oral doses of Penicillin G or phenoxy-methyl penicillin.

Synthetic Newer Penicillins: Due to the emergence of penicillin resistance, newer penicillins, not affected by Penicillin β lactamase, have been synthesised. One of the enzymatic breakdown products 6-*amino-penicillanic acid*, is utilised as starting material. Some of the clinically useful preparations, are:

Methicillin or 2.6 dimethoxyphenyl penicillin: It is not inactivated by penicillin β lactamase and is therefore useful against *S. aureus* resistant strains. It is given parenterally, and its antibacterial spectrum resembles that of older penicillins.

Phenethicillin—It is an acid-stable compound, well absorbed from the G.I. tract. It produces much higher blood levels after oral administration than penicillin G or V.

Cephalosporin N: A penicillin preparation with different antibacterial spectrum. It is less effective against *S. aureus* but very effective against *S. typhi*.

Dosage Forms: Because of the short duration of action and difficulties inherent in parenteral administration, like insulin, a large number of dosage-forms are available. These roughly are—. *Parenteral*—crystalline, and repository forms, 2. *Buccal*, 3. *Topical* and 4. *Inhalation* forms.

1. *Parenteral:*
 - (a) *Crystalline penicillin:* (aqueous), *Dose:* 1-2 lac units/IM/4 hrs.
 - (b) *Procaine Penicillin:* (Aqueous suspension), *Dose* 4 lac units/I.M./24 hrs.
 - (c) *Procaine penicillin in oil:* *Dose:* 4 lac units/I.M./48 hrs.
 - (d) *PAM:* Procaine penicillin in oil with aluminium monostearate 2%; *Dose:* 3 lac units/I.M./72 hrs. It is suitable for use in syphilis.
 - (e) *Benzathine Penicillin (Vicillin)* with ethylene diamine: *Dose:* 1.5 mega units/I.M./1-4 weeks.

The last three are '*repository forms*', from which, penicillin is gradually released, producing sustained action. Besides the above, efforts are being made to combine penicillin with *vasoconstrictors* and use *penicillin esters*, for slow liberation of penicillin by esterase. *Caronamide* a synthetic compound, also delays the penicillin excretion by tubular blocking. In a dose of 3 gm/3 hrs, it has been found to produce a blood concentration of 15 mg% and facilitate C.S.F. diffusion.

2. *Inhalation*: (a) Penicillin dust and (b) Penicillin aerosol. They produce high local concentrations and are used for upper pulmonary tract infections. They have to be supplemented by parenteral penicillin.

3. *Topical*: The calcium salt, which is comparatively less irritating, is available in different forms—cream, ointment, trochiscus (100 units) and unguentum (1000 units/gm.), for topical application.

4. *Buccal*: Still not very satisfactory, requiring 3-4 times greater doses. Benzathine Penicillin, Phenoxymethyl Penicillin or Penicillin V or Peni V oral, vicillin K, are used for mild infections and throat troubles. *Compressed tablets* of 0.5-1 lac unit of penicillin G, with 0.5 gm. trisodium citrate or CaCO_3 . Aluminium salts of penicillin with sodium benzoate, are also used.

Assay: Of great importance, in view of its potency, which is expressed in *units*.

(a) *Cup-plate method*: Inhibition of growth of *S. aureus* over a zone of 24 mm. diameter, in agar plate, represents *one unit*. Inoculation of media is done with a cylinder, and the growth is read in a penicillin zone-counter.

(b) *Serial dilution method*: is carried out in liquid medium in 10 fold dilutions, inoculated with organisms.

(c) *Chemical semi-micromethod*: The amount of penicillin is calculated from the weight of the N-ethylpiperidine derivative.

Unitage: Na penicillin contains 1667 I.U. of activity per mg. or 20,000 units of activity in 12 mg. of the powder.

Metabolism: This is important in view of absorption, distribution and excretion peculiarities of this antibiotic. Its *absorption* is usually rapid though somewhat variable, with the mode of use. With crystalline, penicillin, the peak concentration is maintained for 3-4 hrs. only. Penicillin is *distributed* throughout the body, because of its ready permeability in most of the tissues. There is high concentration in liver, bile, lungs and intestine, but less so in C.S.F., joints, pleural and

pericardial fluids and also in bone-marrow. It crosses the placental-barrier but not the blood-brain barrier, easily. About 60% of the drug is excreted in urine and usually rapidly, partly as penicillin and partly as decomposition product. 80% of penicillin is *excreted* by the renal tubules, at which level, *caronamide* competes with it and the excretion is delayed.

Action: For chemotherapeutic and antibiotic drugs, the general pharmacological actions are not of much significance. *Specific actions* on infective organisms, are the essential points for consideration.

ANTIBACTERIAL SPECTRUM

Definitely Sensitive	Moderately Sensitive	Resistant
<i>Staphylococcus aureus</i> and <i>albus</i> . <i>Streptococcus B-haemolyticus</i> . <i>N. meningococci</i> .	<i>Actinomyces</i> . <i>C. diphtheriae</i> . <i>Sterptococcus viridans</i>	<i>E. Coli</i> , <i>B. typhosus</i> , <i>B. Pestis</i> , <i>Shigella</i> and <i>Pro-teus</i> . <i>M. tuberculosis</i> : <i>H. influenzae</i> . <i>H. pertussis</i> . <i>M. leprae</i> . Rickettsia, certain viruses and fungi.
<i>N. Gonococci</i> . <i>D. pneumoniae</i> . <i>T. pallidum</i> . <i>T. partenue</i> .		

Optimal Blood Level: A concentration of 0.3 unit/ml is usually adequate for most of the infections. This is produced by 3 lac units. A good deal of penicillin is bound on blood proteins, which cannot be detected unanalytically. Crystalline penicillin—one lac units, and Procaine penicillin—3 lac units, would produce an initial blood level of 2-3 units/ml. in the first hour and thereafter, 0.3 units/ml. for 12 hours.

Toxicity: Though it was initially considered to be *atoxic*, with a safety margin of 10-20, the drug is capable of producing minor toxic reactions, as well as, terrific hazards, in certain cases, besides the problem of drug resistance, which is also of considerable significance. *Incidences of untoward reactions*—vary with the type of preparation, and its route of administration. In general, parenteral Procaine penicillin G, produces the highest reactions,—5%; Aqueous penicillin 2.5% and benzathine penicillin 0.3%.

1. *Hypersensitivity reactions:* (i) Skin rashes and contact dermatitis (ii) Acute glossitis, stomatitis, black tongue from penicillin lozenges or trochiscus, (iii) Fever, eosinophilia, *acute anaphylactic or anaphylactoid reactions* and Arthur's phenomenon.

2. *Toxic reactions*: These also depend on the mode of infection and preparations used—(i) local inflammatory reactions (ii) thrombophlebitis, (iii) changes in intestinal flora (iv) Jarisch—Herxheimer reaction, all have been reported, but they are somewhat of theoretical importance now. Some of these occur *immediately*, others within *a week* of the injection.

3. *Resistance formation*: is of the same type as with sulphonamides and other drugs. The staphylococci are more frequently implicated and there are always greater incidences of resistance formation, in the hospital staff and patients.

THERAPEUTIC CONSIDERATIONS

These are numerous and often unassailable by any other therapy, when penicillin is actually indicated.

Pneumococcal Infections: It is the agent of choice for all types of pneumococcal infections.

- (a) *Pneumonia*: In uncomplicated case—(i) Crystalline Penicillin G—3-5 lac units/6 hourly I.M. for 5 days (ii) Procaine Penicillin—6 lac unit I.M., daily for 5 days or (iii) Phenoxymethyl Penicillin—250—500 mg/6 hours O.S.

With this therapy, the mortality and morbidity rate has come down to 0.7% only. The patient is afebrile in 2-3 days and the risk of any further spread of the infection, its complications and even the severity of the disease, are under full control now and one is hardly worried about its prognosis any more.

- (b) *Empyema*—a rarity these days and needs Penicillin—1 million units I.M/6 hourly and 0.5—1 lac units, diluted in 50-100 ml of normal saline, once/day, intrapleurally.
- (c) *Meningitis*: The mortality rate has been reduced from 100% to about 10-20%. Penicillin G—30,000 units in 10 ml. saline, intrathecally, every 12 hours/three doses and also I.M./4 hourly, in doses of 3 to 4 lac units. The therapy is to be continued for 2 weeks.

Streptococcal Infections: Penicillin has produced a veritable conquest of streptococcal haemolyticus and thus of puerperal sepsis, peritonitis and cellulitis.

- (a) *Pharyngitis and scarlet fever*: Phenoxymethyl penicillin—2-4 lac

units, every 8 hours, orally or procaine penicillin G—6 lacs units I.M./day, for 10 days.

- (b) *Meningitis and pneumonia*: Penicillin G 2-3 million units I.M. or I.V./6hrs. for 2 weeks.
- (c) *Otitis media and mastoiditis*: For adults: Phenoxymethyl penicillin—4 lac units orally/6 hours or 1-2 million units I.M./6 hrs., for 2 weeks. For children: 5 lac units I.M./4 hours, for 2 weeks.
- (d) *Acute and subacute streptococcal endocarditis*: Penicillin G—2-3 million units/I.M./6 hrs, for 4 weeks.

Staphylococcal Infections: A real triumph over sulphonamides and the best drug, so far known, for staphylococcal pneumonia, empyema, meningitis, osteomyelitis, carbuncle, furunculosis and thrombophlebitis. Penicillin G, I.M. is the therapy of choice for penicillin sensitive staphylococci. *Total dose*: 10 million units divided into 4-6 equally spaced doses.

When the infections are due to *Penicillin G—insensitive strain*, any one of the following may be tried: (i) *Methicillin*: 6-12 gm./day I.M. (ii) *Oxacillin* 1 gm, orally, every 4-6 hours or 0.5 gm. I.M., every 6 hrs. (iii) *Nafcillin*: 1 gm/6 hourly orally or I.M. for adults and 100 mg/kg./day in divided doses, for children.

Meningococcal Infections: Penicillin G—1 million units I.V., every 2 hours, for 12-14 days along with *sulphadiazine*, which diffuse into the C.S.F. fairly satisfactorily.

Gonococcal Infections: In agent of choice and bacteriological cure in 24 hrs. has been reported.

- (a) *Gonorrhoea*: *Acute urethritis*: 6 lac units of Procain penicillin G, I.M./day, for 2-3 days in males and 5-7 days in females or 1.2 million units of *Benzathine penicillin G*. I.M. *Prostatitis, seminal vesiculitis, or epididymitis*: 6 lac units of procain penicillin 6, per day, I.M. for 1-2 weeks. In *females* with involvement of internal genitalia, 4-6 million units of Penicillin G, I.M., in divided doses, per day, for 10-14 days.
- (b) *Arthritis*: 5-10 million units of penicillin G, I.M. for 2 weeks. *Endocarditis*: 1-3 million units, every 6 hrs/4-6 weeks.
- (c) *Ophthalmia neonatorum*: It is readily cured by parenteral and local uses of *Procain penicillin*—3-6 lac units I.M./day, plus local instillation of Penicillin G in saline or as an ointment, frequently.

Syphilis: Already discussed in Chapter 42.

Actinomycosis: Penicillin G, 1-20 million units, I.M. per day, for 6 weeks.

Diphtheria: No evidence of modifying the incidence, course or complications of the disease and *specific antitoxic serum*, is the only effective treatment, for diphtheria. However, penicillin clears the acute and chronic carrier states, in 3-4 lac units/day, I.M./10-12 days.

Anthrax: Penicillin G—5-10 million units I.M., in divided doses/day, for 2 weeks.

Erysipelas: A single injection of 1-2 million units of *Benzathine penicillin*, is sufficient. When endocarditis is present, 2-20 million units, I.M./day/4-6 weeks, are needed.

For all these conditions, penicillin should be used only for the susceptible strains and at optimal dose level, producing effective concentrations, in the blood. It should be continued till the infection is completely controlled.

Prophylactic Uses: (a) Suspected wounds (b) Surgical operations (c) Delivery cases, (d) Suspected ophthalmia neonatorum.

It is advisable to try penicillin in all sulpha resistance cases. Its failure may indicate—(a) wrong diagnosis (b) inadequate doses (c) loss of potency (d) inaccessibility of the drug to the affected region, due to necrotic tissues, (e) acquired penicillin resistance. The drug should not be used unnecessarily, as at present. It is no more a *panacea* than any other, for all types of infections. The problem of *mounting drug allergy*, should make one think about the role of modern drugs, in its genesis.

STREPTOMYCIN

Another important antibiotic, isolated by Waksman in 1944, from the family of *actinomycetes*, a rich source for offering streptomycin, cycloserine and neomycin. The family of *actinomycetes*, comes in between the moulds and bacteria, in their characteristics.

Chemistry: (a) A submerged culture of *streptomyces griseus*, in a medium containing dextrose, casein digests and inorganic salts, purified by adsorption and crystallised as calcium chloride complex,

(b) *Chemically*, it is an amino base, forming water soluble salts, behaving like a glucoside, which on hydrolysis, yields *streptidine* and *streptobiosamine*, the entire molecule, being necessary for the antibiotic activity.

(c) *Dihydrostreptomycin* is prepared by catalytic hydrogenation of the aldehyde group, in streptomycin.

Preparations: Streptomycin SO_4 , HCl or double salt of CaCl_2 are in use. *Streptoducine* is a mixture of streptomycin and dihydrostreptomycin sulphate, in equal parts.

Assay: (a) *Biological:* On *E. Coli*, (b) *Chemical:* Colorimetric and fluorometric for estimation in body fluids. The first test is quicker but the last one is more sensitive.

Metabolism: Its absorption from the G.I. tract is nil or insignificant, but it produces local antimicrobial action. The maximum absorption takes place after an I.M. injection and the peak blood level is attained in 2-3 hours, declining in 12 hours. It is readily distributed in body fluids, ascitis and pleurasy fluids but inadequately in C.S.F. Over 60% of the drug is excreted by glomerular filtration, in 48 hours.

Antibacterial Spectrum: It is the most effective drug for acid-fast, *micobacterium tuberculosis* and *lepra bacillus* and also for gram negative organisms of *P. pestis* and *E. Coli*, which are insensitive to penicillin. It is more effective in *invitro* than in *invivo* experiments and in view of resistance formation, its use is restricted to certain conditions only, after appropriate sensitivity tests.

<i>Highly Sensitive</i>	<i>Moderately Sensitive</i>	<i>Resistant</i>
M. tuberculosis	Shigella	N. gonorrhoea
Lepra bacilli	H. ducrey	Pyogenic infections
Brucella	V. Cholerae	Beta haemolytic-
H. influenzae	K. granulamata	streptococci
P. pestis		Fungi, rickettsia &
B. proteus	E. coli	viruses
B. pyocyaneus		

Toxicity: (a) Streptomycin is a *neurotoxic* drug, affecting vestibular, cerebellar and oculomotor functions, resulting in giddiness, ataxia, loss of rotational nystagmus. The *vesti-*

bular damage is partially compensated by visual and kinesthetic sensations. *Dihydrostreptomycin* is more toxic for the cochlear division of the 8th nerve, producing tinnitus and deafness.

- (b) The other side-effects are—severe headache, abdominal pain, skin eruptions, arthralgia and agranulocytosis.
- (c) The vestibular disturbances are less serious than the cochlear damages and consequently, for any long term therapy, streptomycin is preferred to dihydrostreptomycin.

- Dose:**
- (a) In *T.B.*—0.5—1 gm. I.M., for 12 months to 1½ years. In *fulminating tuberculosis*—0.25-0.5 gm/ml. I.V., followed by I.M. injections.
 - (b) *Oral* streptomycin is usually given in double doses of —0.5-1 gm/6 hrly. for bacillary dysentery and surgical sterilisation of the gut.

- Uses:**
1. *Tuberculosis:* All types of pulmonary and extra pulmonary conditions—exudative, fibrocaseous, miliary, bone, mucous membrane and kidney.
 2. *Other infections:* (a) *Urinary tract infections*—the causative organisms being *T.B.*, *E. coli*, *proteus*, *pseudomonas salmonella*, *streptococcus foecalis*. The urine becomes sterile in 75 % of the cases.
 - (b) *Peritonitis*, *meningitis*, *endocarditis*. These are usually caused by gram negative, penicillin resistant but streptomycin sensitive organisms.
 - (c) *Pneumonia* caused by *K. pneumonia* and *Friedlander's bacillus*. *Dose:* 2-3 gm/day, for 5-10 days.
 - (d) *Intestinal infections:* 2-3 gm/day for 7-10 days.
 - (e) *Brucellosis*, *granuloma inguinale*, *tularaemia* and *plague*.

It is customary to try streptomycin in cases not responding to penicillin. However, one has to beware of the risk of worst type of *resistance formation*. It is therefore better to keep the drug in reserve for the treatment of tuberculosis only. *Streptocaine* may be used if the combined action of penicillin and streptomycin is desired.

BROAD SPECTRUM ANTIBIOTICS

As the name suggests, this group of drugs was designed to possess wider range of activity than the narrow spectrum ones, with lesser

toxicity and resistance formation liabilities. As these objectives are, to an extent, fulfilled by these drugs, they are known as, *Broad Spectrum Antibiotics*.

Classification: They comprise the following 2 groups of drugs:

I. *Chloramphenicol* or chloromycetin.

II. *Tetracyclines* and their 4 important derivatives.

The broad spectrum antibiotics are suitable for oral administration, in the form of capsules, masking their bitter taste and local effects, on the stomach. Their antimicrobial actions are not limited to the gram + or - organisms only, but also encompass *viruses* and *rickettesial bodies*, which latter, are the causative agents for typhus, rocky mountain spotted and 'Q' fevers, not amenable to sulphonamide and narrow spectrum antibiotic therapies. Further, they induce less microbial resistance and act even on penicillin and streptomycin resistant organisms.

CHLORAMPHENICOL

An important antibiotic, isolated by Burkholder, in 1947, from *Streptomyces venezuellas* and was the first to be synthesised. It is an aromatic nitro compound, containing non-ionic chloride. It contains a nitrobenzene moiety and is a derivative of dichloroacetic acid. (Plate XL, Fig. 108).

It occurs as colourless needles, of elongated plates, *bitter* in taste, slightly soluble in water but very soluble in ethanol. It is extremely stable, unaffected over a pH range of 2.0 to 9.0 and resists boiling.

Assay: The concentration of chloramphenicol in the biological materials can be determined *chemically* or by *microbiological assay* procedures. The former, however, does not differentiate between the biologically active and inactive degradation products.

Metabolism: (a) It is rapidly absorbed from the G.I. tract, the peak plasma concentration is reached in about 2 hours and the drug disappears from blood in 12-18 hrs. About 60% of the drug is bound to the plasma albumin.

(b) It is uniformly distributed in the body fluid and is also present in C.S.F., bile and milk. It crosses the placental barrier, producing a foetal blood concentration of 30—80% of the maternal blood level.

(c) The drug is inactivated mainly in the liver and is rapidly excreted

in urine, where its concentration is 20 times higher than in the plasma. About 80-92% of the drug is excreted in 24 hours, in unaltered form, by glomerular filtration and a small quantity, as inactive degradation product, by tubular secretion.

Antibacterial Spectrum: (a) It possesses a wide spectrum of bacteriostatic activity and is the drug of choice for *salmonella infections* and *typhoid fever*.

(b) It is also effective against a large number of gram positive and negative organisms, rickettsia, certain viruses and *T. pallidum*.

(c) It is ineffective against pathogenic yeasts and fungi.

(d) It is believed that chloromycetin interferes with the synthesis of proteins at the stage of tryptophane incorporation. It is bound to 30 S ribosomes and so prevent access of amino acetyl-t-RNA.

(e) It is partially inactivated in the body and causes minimum resistance formation for viruses and rickettsia.

Dosage Forms: *Capsules* of 50, 100 and 250 mg., with an *initial dose* of 0.5 gm, followed by 0.25 gm/3 h. The palmitate suspension is devoid of the disagreeable bitter taste and is used for children, in 125 mg/drachm doses.

Toxicity: G.I. upset, dryness of mouth and sometimes *dangerous agranulocytosis* and vitamin B deficiencies. The marked *bone marrow aplasia* caused by the drug, is a limiting factor in its use, in most of the conditions, needing prolonged therapies.

Therapeutic Uses: These are limited to those infections, in which, the organism is highly susceptible to this antibiotic.

Typhoid fever: It is the drug of choice for this condition. *Dose:* 2 gm. initially, followed by 1 gm., every 6 hours, for a week or 10 days. The therapy has completely changed the outlook of this disease. The patient becomes afebrile in 48 hours, all complications practically eliminated and the course is reduced to 7-10 days only. However, it does not induce any immunity and relapses are not infrequent.

Rickettsial diseases: The drug produces dramatic effect in these conditions also. The first dose for an *adult* is 50 mg/kg., followed by 1 gm. every 8 hours, till improvement occurs and fever is absent for 24-48 hours. In *children*, the dose is 25 mg/kg., divided in equal doses, every 6-8 hours.

Urinary tract infections: *Proteus vulgaris*, *K. pneumoniae*, *H. influenzae* and *P. S. aeruginosa* are more sensitive to chloramphenicol than

other agents. *Dose*: 0.5 gm. orally, every 6 hours, for 7-10 days. The dangerous bone marrow depression produced by the drug, is however to be borne in mind. In *E. coli* infection of the urinary tract, it is used only in cases where other measures of therapy fail.

Staphylo and *streptococcal* infections which are resistant to other antibiotics may sometimes need this drug. Its use in *atypical pneumonia*, *typhus fever*, *brucellosis* and *whooping cough*, is still advocated, though its blood toxicity is a limiting factor.

Meningitis due to H. influenzae: When used in combination with full doses of sulphonamides, it gives excellent results. *Total daily dose*: 50 to 75 mg/kg, divided in four doses, I.M., every 6 hours, for 2 weeks.

TETRACYCLINES

The group comprises 4 important members, obtained from the *soil* organisms of *streptomyces* and are most popularly used and abused.

1. *Chlortetracycline* or *Aureomycin*.
2. *Oxytetracycline* or *Terramycin*.
3. *Tetracycline* or *Achromycin*.
4. *Demethyl chlor-tetracycline* or *Ledermycin*.

The *first two* members, were obtained from *S. aureofaciens* and *rhimosus*, respectively, between 1948-54, the *third*, was produced semi-synthetically by catalytic hydrogenation of the first and the *last*, from a mutant of *S. aureofaciens* in 1957 only. Their *chemical* nature is shown in *Plate XL*, Fig. 109. It may be observed that they have a common basic structure of *hydronaphthaleine*, aureomycin possessing a *Cl* atom at *ring 1* and terramycin an *OH* group, at *ring 3*. All of them are amphoteric i.e. both basic and acidic in nature.

They are available as 250 mg *capsules*, 25 and 50 mg/ml. *suspension*, and 0.1-0.5 gm. *ampoules*, for parenteral injections. All of them are available as hydrochloride but tetracycline, as phosphate salt also. The calcium compound of chlorotetracyclines, is available for topical uses.

The crystalline bases are faintly yellow, odourless and bitter, very little soluble but the SO_4 and HCl salts are soluble in water. The solutions of the *first two* are very unstable, lasting for 3-4 days only, while that of *achromycin* may last for 3 weeks, at a pH of 7. The *last* is stable in a wide range of pH. These drugs are assayed microbiologically from the body fluids, which are not highly quantitative.

- Metabolism:** (a) All of them are readily absorbed from the G.I. tract (stomach and upper small intestine only) producing the peak blood concentration in 2-4 hours, lasting for 12-24 hours. Milk products, aluminium hydroxide gel, calcium and magnesium disturb their intestinal absorption. *Chlortetracycline* is absorbed more irregularly and *demethylchlortetracycline* has a more regular and sustained absorption and plasma concentration, than others.
- (b) All of them are widely *distributed* in the body fluids, excepting C.S.F., which gets half the blood concentration and in the case of demethylchlortetracycline, even less. They are bound to plasma proteins in varying degrees (chlortetracycline—70%, demethyl chlortetracycline—50% and others 25% only).
- (c) Their metabolic endproducts are not known but the excretion takes place in urine and faeces.

- Common Properties:** (a) All the members of the group are *orally* effective with better and more sustained blood levels, compared to penicillin.
- (b) On prolonged use, they alter intestinal flora and induce *moniliasis*
- (c) They are all *irritant* for the G.I. tract, the worst being *terramycin* and the mildest *achromycin*.

Antimicrobial Actions: These affect a very wide range of organisms:

- (a) Gram + & —organisms, overlapping penicillin, streptomycin, chloromycetin and also those which are resistant to them.
- (b) They inhibit the growth of rickettsia, amoebae, mycoplasmae, viruses, lymphogranuloma, psittacosis, inclusion conjunctivitis and trachoma, rocky mountain fever, Q fever, typhus, measles, herpes, polio and brucellosis.
- (c) They also act on fungi, parasites, large viruses and most of the intestinal flora.

Their *advantages* are—(a) less resistance formation and (b) oral administration but the *disadvantages* are: (a) moniliasis and (b) cross-resistance formation. This is applicable to all the members of the group.

Mechanisms of Action: Not yet definitely established. Some of the readily acceptable ones are: (a) Active chelation of cations (b) Inhibition of essential enzymes (c) Suppression of protein synthesis (d) Binding of Ca, Mg, Mn and inhibition of oxydative phosphorylation, in the mitochondria, referred earlier.

- Untoward Effects:** (a) *Hypersensitivity reactions:* Skin rashes, urticaria, angioneurotic oedema, anaphylaxis, burning of the eyes and eosinophilia. They also cause cross-sensitisation amongst them.
- (b) *Toxic irritating effects:* (i) *Gastro intestinal tract*—oxytetracycline chlortetracycline—tetracycline—dimethylchlortetracycline, in descending order of severity. They produce nausea, vomiting, diarrhoea, stomatitis and brown colouration of teeth in children and also superinfection.
- (c) *Blood changes:* atypical lymphocytosis, thrombocytopenic purpura and *phototoxic reactions* on the skin, produced by *dimethylchlortetracycline* and also delayed blood coagulation.
- (d) *Liver and renal damage:* oxytetracycline and tetracycline are the mildest. In renal dysfunction cases, they are to be used with caution.
- (e) Other toxic manifestations, reported are: (a) Increased intracranial pressure, (b) Faconi's syndrome with nausea, vomiting, polydipsia, polyurea and glycosurea and (c) Teratogenic defect in foetus, if given during pregnancy.
- (f) Biological effects like loss of weight, increased urinary riboflavin and faecal fat excretion, have also been reported.

TETRACYCLINES COMPARED

NAME OF DRUGS	Chlortetracycline or Aureomycin.	Oxytetracycline or terramycin	Tetracycline or achromycin	Demethylchlortetracycline or declomycin.
SOURCE	Strep. aureofaciens.	Strep. rhimosis.	Semisynthetic	Mutant strain of aureofaciens.
STABILITY	Least stable.	Stable	Most stable.	Stable.
ORAL ABSORPTION	Limited.	Limited.	Satisfactory.	Limited but regular and sustained.
EXCRETION IN URINE	10-15%	10-35%	20-55%	10-20%
SPECIAL ANTI-BACTERIAL SPECTRUM BESIDES COMMON ONES	Strepto and pneumococci.	Pseudomonas.	Proteus.	Twice as potent as others against all the organisms
TOXICITY	+	±	Least toxic.	±

THERAPEUTIC USES

Though very wide, covering a large field of infection from divergent groups of organisms, detailed hereafter, it is a real problem to choose any individual member predilectively, as all of them vie with each other very closely, in their claim for use in a particular condition. They are of *proven value* in-spotted fever, typhus and Q fever, brucellosis, subacute bacterial endocarditis, urinary tract and ocular infections, venereal diseases and amoebiasis.

Rickettsial Infections: *Various types*—rocky mountain spotted fever, murine and scrubtyphus and Q fever, spread by the arthropods—lice and tick. The infection is characterised by continuous fever, rash, lymphadenitis and ulceration. Often they occur in epidemic forms lasting for a fortnight and having a high mortality rate.

Treatment comprises the use of a *broad-spectrum* antibiotic, along with *corticosteroids*, *chloramphenicol*—50 mg/kg *initially*, followed by 5 gm in divided dose and thereafter, 1-2 gm/daily till the patient is afebrile. The therapy often produces dramatic result. For *prophylaxis*, D.D.T. and vaccines are recommended.

Q. Fever: In this disease, there is a sudden onset, headache and interstitial pneumonia. Sulphonamides and narrow spectrum antibiotics have no place in its therapeutics but *chloramphenicol* and *tetracyclines*, are effective.

Psittacosis: It is a viral disease, in which, fever with fatal pneumonia and encephalitis, can occur. The infection is transmitted by birds. *Chlortetracycline*: 4 gm. daily, for two days and 2 gm. daily, thereafter, until recovery, is the treatment of choice. The treatment should be continued for a week or two.

Lymphogranuloma: For the *acute type*, *sulphathiazole* or *sulphadiazine*: 5 gm, daily, in divided doses for 5-10 days, *tetracyclines*: 1 gm/6 hours for 7 days or *tri-acetyl oleandomycin*—1 gm/twice a day, for 5 days, gives the best results. There is reduction of the bubo in 4 days and disappearance of lymphnodes, within a week.

Inclusion Conjunctivitis and Trachoma: *Sulphadiazine*—2 gm. initially and then 1 gm q.d.s., for one week. Simultaneously, *chlortetracycline* or *tetracycline* ointment or lotion and also sulphacetamide, are recommended.

Mycoplasma Infections: In this, there is a diffuse type of inflammation of the lungs without consolidation, with resultant fever, dry unproductive cough and malaise, lasting for 10-14 days. There is primary, atypical type of pneumonia. *Chlortetracycline* 300 mg/t.d.s. for 6 days, produces marked improvement.

Brucellosis: or *Malta Fever*, due to *B. abortus*, is transmitted through goat's milk. There are intermittent wavy types of pyrexial bouts, with toxæmia, splenomegaly, malaise and afebrile intervals. Its treatment comprises the use of *streptomycin*: 1-2 gm I.M. daily, *sulphadiazine*: 4-6 gm. daily/os and *tetracycline*: 2 gm/daily/os for 3 weeks.

Tularæmia: This is a highly infective condition, caused by *pasteurella*, present in rodents. The clinical picture resembles plague and is characterised by an ulcer at the site of the infection. As therapeutic measure, *streptomycin* and dihydrostreptomycin—500 mg/8 hrly, for 3 days, *chlortetracycline* and *chloramphenicol*—are useful.

Venereal Infections: For gonorrhoea and granuoma inguinales, *tetracycline*: 0.5 gm. or *demethylchlortetracycline*: 0.3 gm/6 hrs., for a few days. *Sulphonamides* are preferred for the management of chanroid granuloma. It also responds to streptomycin, chloramphenicol and tetracyclines. The treatment should be continued for 2 weeks.

Urinary Tract Infections: From proteus and pseudomona infections, *tetracyclines* are never to be used as routine procedures but only if the organisms are specially sensitive to it. Tetracycline or demethyl chlor-tetracycline (250 mg and 150 mg respectively)/every 6 hours for 7-10 days.

Amoebiasis: A combination of *oxytetracycline*—0.5 gm. orally/every 6 hrs. and chloroquin-1 gm. daily for 2 days and 0.5 gm for the next 18 days, offers fairly good results and acts upon cystic, as well as trophozoite forms.

Results of broad spectrum antibiotic therapy in actinomycosis, leptospirosis, mucococcidiosis and chronic pulmonary diseases, are also fairly encouraging.

OTHER ANTIBIOTICS

It has been customary to designate these antibiotics as *newer antibiotics*. This is not fully correct as some of them are as old as the oldest anti-

biotics. Similarly, it is not appropriate to group them as *minor antibiotics*, because they have been less used than others. They may be considered as *second line* of useful drugs, in cases of resistance or failure of their commonly used counterparts.

They represent a large number and widely different varieties of antibiotics. Some of them have *penicillin type* of spectrum of action—erythromycin, novobiocin, cephalosporin and vancomycin, Neomycin resemble *streptomycin* in action; oleandomycin, kanamycin and puromycin possess *broad spectrum* of activity and used in intestinal amoebiasis, while polymyxin, bacitracin and tyrothricin are chiefly meant for *local applications*.

ERYTHROMYCIN

An orally effective antibiotic, isolated in 1952, from *streptomyces erythreus*. It is a *macrolid* antibiotic with a large lactone ring. The aqueous solution is unstable. It is not affected by penicillin. It is effective against staphylo, strepto, pneumo; neisseria, H. influenza, clostridium, brucella, rickettsiae, trepanoma and B. proteus organisms, susceptible to penicillin G, but not to streptomycin. It is absorbed from the upper part of the G.I. tract and produces a peak blood concentration in 1-4 hours. It diffuses into the body fluids excepting the brain, which gets only 1/8th of the plasma concentration. *Oral preparations*: Erythromycin stearate capsules of 125-250 mg. and *liquid suspension* 25 mg/ml. *Daily dose*: 2-4 gm. *Parenterally*—erythromycin glucuhaptonate is used.

Toxic effects: (a) Hypersensitivity reactions (b) Cholestatic hepatitis and (c) Irritating effects on the mucous membranes.

Uses: (a) Staphylo and other coccal infections—scarlet fever, erysipelas and pneumonia. (b) Diphtheria, particularly the carrier stage, 500 mg/6 hrs/2 weeks—100% result. (c) Syphilis, gonorrhoea and tetanus. (d) Prophylactic use in rheumatic fever and neonatal infections.

Cephalosporins: It was isolated in 1956, for overcoming the deficiencies of *penicillin*, to which, it is closely related. It has a lactam ring and when given parenterally it passes into the body fluids and then excreted in urine within 6 hours. It is not affected by penicillinase and is effective against penicillin resistant *staphylococcus aureus*. It is ineffective against pseudomonas. It is contained as 1 gm. of sodium salt in 60 ml.

ampoule, to be diluted with 4 ml. of sterile water and given I.M. Its toxic effects are minimum.

Oleandomycin: This is obtained from *streptomyces* and is active against gram positive and negative organisms and rickettsial infections. Given orally, it is effective in the treatment of pneumococcal, streptococcal and staphylococcal infections.

Triacetyloleandomycin: A semisynthetic antibiotic, obtained by the esterification of *oleandomycin*. It is better absorbed than others, producing higher blood levels. It is excreted through kidneys in an active form and is used in the treatment of urinary tract infections. It produces cross-resistance with erythromycin. Dose: 250-500 mg. q.d.s. Side effects—nausea, vomiting, diarrhoea and skin reactions.

NEOMYCIN

It was discovered by Waksman, in 1949 from *Streptomyces fradiae* and is a complex of 3 compounds. It is a polybasic, water soluble, thermostable substance, readily forming salts.

It is a broad spectrum antibiotic, effective against a number of gram negative organisms—e.g. *K. pneumoniae*, *Pasturella*, *Salmonella*, *Shigella*, *H. influenzae*, *V. cholera* and *H. pertussis*, *Staphylococcus*, *M. tuberculosis* and *Leptospira ictero-hemorrhagica*. Fungi and viruses are resistant to neomycin. It is poorly absorbed from the oral route but better absorbed after I.M. injection. It is excreted in the urine and faeces.

Preparations: Neomycin sulphate for topical, oral and parenteral administrations. Dose: 0.5 gm. tabs, solution and also ointments and powder. Intramuscularly, it is given in 0.5 gm. every 6 hours and orally 4-8 gm. daily, in divided doses.

Toxic effects: (a) Hypersensitivity reaction. (b) Renal damage. (c) Deafness. (d) Intestinal malabsorption (e) Superinfection and (f) Sprue like syndrome.

Uses: (a) Topical application for burns and infected dermatosis. (b) Preparation of bowels for surgery and (c) Systemic infections.

Puromycin: A broad spectrum antibiotic, derived from *Streptomyces rhimosus* and having the same spectrum of activity as *neomycin*. It is poorly absorbed from the G.I. tract. It is available as capsules of 250 mg. and suspensions of 125 mg/5 ml. Dose: 1 gm. every 6 hrs.

for two days, followed by 1 gm/12 hrs. For the treatment of salmonella and shigella infections, the dose is 35 mg/kg/day for 7-14 days. Its *side effects* are—nausea, abdominal cramps and diarrhoea. *Uses*: Hepatic coma, preparation of patients for bowel surgery, salmonella gastroenteritis and carriers, bacillary dysentery and amoebiasis.

KANAMYCIN

An antibiotic, derived from *Streptomyces kanamyceticus*. It is polybasic, water soluble and resembles *neomycin*. It has a broad range of activity against both the Gram + and — organisms—*E. coli*, *K. pneumoniae*, salmonella, shigella, *Vibrio cholera*, *Neisseria*, *staphylococcus aureus* and *M. tuberculosis*. The *pseudomonas*, enterococci, clostridia, yeast and fungi, are resistant to it.

It is poorly absorbed from the G.I. tract. The peak plasma concentration of 20-35/ug/ml. is reached in 1 hr., after I.M. administration, lasting for 6-12 hrs. It is not bound to the plasma proteins and no accumulation, usually occurs, if the renal functions are normal. It diffuses into pleural, ascites, synovial and peritoneal fluids, as well as, bile.

Preparations: Kanamycin sulphate—injectable solution containing 250 mg. in 2 ml. *Oral dose*: 6-8 gm/day but the I.M. route is preferred.

Side Effects are the same as with others: hypersensitivity reactions, pain, sterile abscess, diarrhoea, oto and nephro toxicity and also curare like paralysis.

Uses: *Staphylococcus*, *E. coli* and *K. pneumoniae* infections. It is also used in tuberculosis and abdominal surgery.

Polymyxins: (a) A group of polypeptide antibiotics, derived from *B. polymyxa*, and designated as Polymixin A, B, C, D & E, each containing a fatty acid residue, varying from one another in their amino acid content of leucine, phenylalanine, thianine and serine. (b) It is bactericidal for the gram negative organisms, including *P. aeruginosa*. (c) Only polymyxin B is used therapeutically, others being quite toxic for kidneys and nervous tissues. (d) It is used for the treatment of burns and wounds and also for meningitis due to *H. influenzae*.

Colistin: It was isolated from *B. colistinus*, polymyxia and subtilis and is closely related to polymyxins. It is bactericidal for *E. coli*, *pseudomonas*, *K. pneumoniae*, *H. influenzae* and shigella. It acts by alteration in the permeability of the bacterial cytoplasmic membrane.

Its side effects—dizziness, ataxia, paraesthesias, proteinurea, haematuria and nitrogen retention. *Dose*: I.M.—1.5 to 2.5 mg/kg. *Orally*: 3-5 mg/kg., in divided doses, as *tablets* or *suspensions*.

Novobiocin: (a) It is obtained from *Streptomyces niveus* and is effective, primarily, against *gram positive* and *gram negative* organisms—*H. influenzae*, *Ps. aeruginosa* and *P. vulgaris*. (b) The antibacterial spectrum is the same as for penicillin and is used for *penicillin resistant* strains of *staph. aureus* and for urinary tract infections from *P. vulgaris*. (c) It is well absorbed, concentrated in liver, secreted in the bile and is reabsorbed again from the G.I. tract. This enables the maintenance of high blood levels, for a long period. *Side effects* are—skin rashes, nausea and gastric discomfort. *Dose*: 0.5 gm/hrs.

Vancomycin: An antibiotic produced by *Streptomyces orientalis*. It is active against *gram positive* bacteria, strepto, straphylo, pneumo, gono and clostridium. It probably inhibits the production of cell-wall mucopeptide, which in turn, suppresses the R.N.A. synthesis.

Preparations: Vancomycin hydrochloride—10 ml. vials, containing-50 mg/ml. solution for I.V. Injection. *Side effects*: Hypersensitivity reactions, phlebitis, and nephrotoxicity. In actual practice, very little used in therapeutics.

Bacitracin: An antibiotic produced by *B. licheniformis* and is a mixture of neutral polypeptide. It is fairly stable and active, mainly against *gram positive* organisms. It has been tried in penicillin resistant organisms but because of its *nephrotoxicity*, its use is now restricted to *local applications* only, for burns, ulcers, wound, abscesses, boils and carbuncles. *Dose*: 10,000-25,000 units, every 6 hrs. in adults and 200-400 units per kg. in children for systemic infections.

Ristocetin: A mixture of ristocetin A and B, obtained from *actinomycete neoadrialurida*. It is not absorbed orally and is therefore given by slow I.V. injection only. It is active against *gram positive* organisms and has been used in the treatment of *staphylococcal infections*, resistant to penicillin and other antibiotics. *Dose*: 1 gm. every 12 hrs. Skin reactions, diarrhoea, fever and in some cases leucopenia also, are observed as *toxic effects*.

Tyrothricin: A mixture of the *gramicidins* and *tyrocidines* groups of antibiotics, obtained from *B. brevis*. It is active against *gram positive*

organisms, even in the presence of serum. It is detergent in nature and is used for *local applications* in the treatment of infected wounds and burns. It is sometimes combined with polymyxin B. or neomycin.

Lincomycin: It is an antibiotic, effective in infections, due to pneumococci, streptococcus pyogenes and staphylococcus aureus. It is also effective in chronic osteomyelitis. *Dose:* 500 mg/os every 6-8 hours.

Gentriamycin: It is quite effective in urinary tract infections due to *E. coli*, *K. lebrilla*, aerobactor and pseudomonas, when used in doses of 0.4 mg/kg. I.M. t.d.s. daily, the dose not exceeding 2 mg/kg. *Ficidin* has been reported to produce good results in staphylococcal infections but the organism rapidly becomes resistant to the drug. *Dose:* 500 mg/os t.d.s. *Fumagillin* along with other antibiotics—puromycin and tetracyclines, has been used in amoebiasis but has almost been withdrawn for reasons of toxicity and doubtful efficacy.

In substance, *Erythromycin* may be considered in pneumococcal pneumonia, diphtheria, anthrax and erysipelas; *Cephalosporin* and *Lyncomycin* in penicillin resistant staphylococcus infections and the former also in streptococcus viridans and nocardia infections; *collistin* and *Gentamycin*, in urinary tract infections from *Ps. aeruginosa* and *B. foecalis*; *Kanamycin* and *Polymixin B* for urinary tract infection and the latter for plague and malignancy also. They 'no doubt' are still to be considered as *second line antibiotics* till more extensive clinical trials have been made. Their main usefulness, besides their spectrum of activity, is in their status in resistant and contraindication cases of other antibiotics.

POLY-ANTIBIOTIC THERAPY

A common temptation, comparable to the polypharmacy of the past, the underlying idea being multipronged attack with minimum risk of resistance, even with less accurate diagnosis. The method, though advocated for tuberculosis, should not be necessary for most, of the other short lasting ailments, as it may eventually expose the organisms to the risk of resistance formation against both. There is no question of combining a potent with a weak antibiotic and it is better, if needed, to use one after another. The antibiotics, as already described, have far-reaching biochemical actions in the body and their indiscriminate use may be harmful. Their uses should therefore be restricted to well indicated and essential cases only.

ANTIFUNGAL ANTIBIOTICS

A new addition resulting from the frequent occurrences of *moniliasis*, as a result of the use of broad spectrum antibiotic therapy. The group also includes one or two antifungal antibiotics used in skin infections. The following drugs are to be considered.

Mycostatin: (a) Also called *nystantin* and *mystechine*, is a combination of mycostatin and tetracycline and is obtained from *Streptomyces nourseae*.

(b) It is obtained from streptomyces and is effective against yeasts and fungi—(i) *Candida albicans* and (ii) *C. neoformans*, both of which, are responsible for the production of moniliasis.

(c) Pale yellow, water soluble powder, partly absorbed from the G.I. tract, producing local action and also sometimes *hypersensitivity* reactions.

(d) The usual *oral dose* is 500,000 units and for vaginal uses, tablets or ointment containing 1,000,000 units.

(e) *Uses:* *Intestinal* as well as, *oral* and *vaginal moniliasis*. For other parts, only topical applications are advocated.

Griseofulvin: (a) It is obtained from *Penicillium griseofulvum*. Due to small particles, it is *readily absorbed* from the G.I. tract and is effective in half concentration. It is *excreted* in the form of metabolites. (b) Its mechanism of action is partly due to the inhibition of synthesis of nucleic acids. (c) *Dosage forms:* (i) Tablets of 125 mg., 1-2 tablets, maximum 5 tabs./os/bid. For *children*—half dose is needed. (ii) The therapy is recommended for 1-2 months, depending on the conditions and findings in the skin. (d) For *local* application, the powder is used. The preparation, *multifungin*, contains boric and salicylic acid, along with it. (e) The *side effects* are usually minimum and of transient and minor nature—headache, gastric discomfort, urticaria and eruptions.

Uses: (a) *Ringworms* of the scalp, (b) Other fungal infections—epidermophyton and trichohyton, (c) *Ineffective* in monilial infections, actinomycosis, histoplasmosis.

Amphotericin B: This is obtained from the *Streptomyces nodosus*. Though it can be given orally also, the absorption is much greater by the parenteral route. *Dose:* 0.5 mg/kg to 1 mg/kg. I.V. in 5% dextrose solution; topically as 1% lotion.

Toxicity: *Acute:* Fever, nausea, chest pain, phlebitis and even ventricular fibrillation. *Chronic:* Anorexia, blurring of vision, purpura, raised blood urea and N.P.N. *Uses:* *Deep mycotic infections:* blastomycosis, histoplasmosis, moniliasis, coccidiomycosis and cryptococcosis.

THERAPEUTIC INDEX

Diplococcal Pneumonia	Penicillin G, Erythromycin.	Whooping cough	Aureomycin
Inflammatory & suppurative conditions	Penicillin G, Cloxacillin Cephalosporin, Lincomycin	Diphtheria	Penicillin G, Erythromycin
Gonorrhoea	Penicillin G, Erythromycin, Ampicillin, Cephalosporin, Tetracyclines	Influenza	Streptomycin, Tetracycline, Sulphonamides
Typhoid and Paratyphoid	Chloromycetin, Ampicillin, Cephalothin	Atypical viral pneumonia	Tetracyclines
E. coli, pyelonephritis	Furadantin, Sulphonamides, Ampicillin, Chloromycetin, Tetracycline	Rickettsial infections	Chloromycetin, Tetracycline
Bacillary Dysentery	Sulphonamides, Tetracyclines Streptomycin	Fungal infections	Mycostatin, Griseofulvin
Urinary tract infections	Chloramphenicol, Tetracycline, Collistin, Kanamycin, Polymyxin B.	Trachoma	Sulphonamides, Tetracyclines
Plague	Streptomycin, Sulphonamide, Tetracyclines	Antineoplastic	Azaserine, Mitomycin Achromycin D DON.
Cholera	Tetracyclines, Chloramphenicol	Gas gangrene	Penicillin G, Tetracyclines

In all these cases, the unavoidable hazard is the *resistance formation*. For this, the customary rule is—(a) In cases of sulpha resistance, to use penicillin for sensitive organisms, (b) In case of penicillin resistance, streptomycin or streptocaine, (c) If the organisms are still resistant, use broad spectrum antibiotics and *finally* newer antibiotics, if necessary, may be used.

CHAPTER

47

CHEMOTHERAPY OF TUBERCULOSIS, LEPROSY AND URINARY TRACT INFECTIONS

THE OLD AND NEW DRUGS—THEIR ACHIEVEMENTS AND PITFALLS. THE
PROBLEM OF DRUG RESISTANCE AND ITS CIRCUMVENTION. CURRENT
THERAPY OF URINARY TRACT INFECTION AND ITS LIMITATIONS.

[Advances in the therapy of tuberculosis and to an extent, of leprosy, the fatal and much despised diseases of the past, have been remarkable in the recent histories of pharmacological achievements.

For *tuberculosis*, the first line of drugs are—streptomycin and I.N.H. and the second line—vioform, cycloserine, kanamycin, tetracycline, PAS, thiosemicarbazone, pyrizinamide and ethionamide. All of them have some degrees of toxicity, particularly streptomycin and dihydrostreptomycin, on the 8th nerve. They also produce drug resistance by adaptive changes and mutation in the mycobacterium. The available drugs can deal with all forms of tuberculosis—fibrocaceous, exudative, miliary, bone, abdominal and meningeal, INH having greater diffusion and penetration than others. Usually, the combined therapy of streptomycin, INH and PAS or thiosemicorbazone, pyrizinamide, ethionamide or cycloserine, is used.

For *leprosy*, the range of drugs is the same, as above, but in practice, DDS, sulphetrone, ACTH and cortisone and rarely hydno carpus compounds, are used. The therapy, perforce, is long, but with effective treatment, clinical improvement occurs in 3-6 months and bacteriological cure, in 1-2 years, depending on the actual stage of the disease when the treatment is started. The treatment is to be continued for about 3 years.

Urinary tract infections: may be from any of large number of organisms—gram positive or negative, bacilli or cocci, pseudomonas, proteus etc. but *E. coli* infection is the commonest.

Drug therapy comprises the judicious use of sulphonamides—sulphasomidine particularly, *antibiotics*—tetracyclines, erythromycin, chloramphenicol and also hexamine, furadantin, mandelic acid and sometimes even autovaccine. For *E. coli*, infection, elkosin, furadantin and tetracyclines are preferred; for *proteus* pyelitis, ampicillin, chloramphenicol and kanamycin; for *aeruginus*, colistin and polymixin. for streptococcus faecalis infection, furadantin and for cocci, erythromycin and penicillin. The results of current therapies, in all these conditions, are remarkably good.]

CHEMOTHERAPY OF TUBERCULOSIS

Any review of antitubercular agents would comprise the following groups of potent, specific drugs.

ANTIBIOTICS

*Major: Streptomycin**Minor: Viomycin, cycloserin, kanamycin, tetracyclines*

CHEMOTHERAPEUTIC AGENTS

*Major: Isonicotinic acid hydrazide**Minor: PAS, thiosemicarbazone, Pyrizinamide, ethionamide*

Judiciously used, these drugs, along with B.C.G. can achieve almost complete control of this erstwhile dreadful disease. Of these various drugs, streptomycin, kanamycin and tetracycline have already been studied. The remaining drugs will be dealt with individually and the therapeutic status of the effective antitubercular drugs, detailed. For obvious reasons, gold which has already been included in the Chapter of antirheumatic drugs, will not be studied here, as with the advent of newer drugs, it has completely lost its place from the therapy of tuberculosis.

Methods of Evaluation: *Toxicity and therapeutic efficiency tests, by in vitro and in vivo experiments in guinea pigs, rats and rabbits, the first being considered to be the megaphone of tuberculosis. The tests employed are:*

- (a) *In vitro* serial dilution technique.
- (b) Mouse survival test.
- (c) Corneal inoculation method in rabbits and mice.
- (d) Clinical trials—pilot and large scale studies.

PARA AMINO SALICYLIC ACID

In 1941, Bernheim, while studying the nutritional requirements of *M. tuberculosis*, observed the role of salicylic and benzoic acids in increasing the O_2 uptake in the bovine strain. Lehman (1943), confirmed the same in the human strain, as well. It was evident that these substances were used as substrate for respiratory activities, by the *M. tuberculosis*. Their structural analogues, paraaminosalicylic acid (PAS), was found to inhibit the growth at a very low concentration—obtainable by oral administration in man, thus acting as a specific antimetabolite. Other workers demonstrated the enhancement of the bacteriostatic effect of streptomycin by PAS in *in vitro* studies and in this manner, the position of the drug as an *adjuvant* to streptomycin, was established, by a series of experimental studies in guinea pigs.

Chemistry and Preparations: White crystalline powder, sparingly soluble, solubility increasing to 15% only, with the Na Salt. P-amino salicylic acid granules, capsules or tablets of 0.3-0.5 gm. each, are used. **Dose:** 10-20 gm/day/os. Sodium salt—2-10%, for instillation into the cavities. The *potassium salt* (*Paskate*) is less irritating for the stomach.

Metabolism: It is rapidly absorbed, uniformly distributed in blood and tissues but not in the C.S.F. It is partially conjugated in the liver and rapidly excreted in urine, in free and conjugated forms. Repeated doses are therefore required for maintaining an appropriate blood level of the drug.

Actions: The drug has weak bacteriostatic but specific action on *M. tuberculosis* and is used as an adjuvant to streptomycin and I.N.H. However, due to the miserably high dose and the gastric irritation caused by the drug, its use is not free from troubles. The resistance formation though slower and weaker than streptomycin and I.N.H., is also an unwelcome feature.

Toxicity: (a) Nausea, vomiting and diarrhoea, relieved by NaHCO_3 and aluminium hydroxide suspensions (b) Allergic pruritus, responding to antihistaminics.

Uses: As an adjuvant to streptomycin in the treatment of different forms of tuberculosis but of late, thiosemicarbazone has been found to be equally effective and cheaper.

ISONICOTINIC ACID HYDRAZIDE

Chemistry and Preparations: A synthetic substance of a simple benzene structure, having a hydrazide (NHCNH_2) grouping. It is also known as *Isoniazid* and *Iproniazid*. White crystalline powder, dispensed as tablets of 50 and 100 mg. for oral use. **Daily Dose**—150-400 mg. in divided doses. Children tolerate larger doses for their age.

Metabolism: (a) The drug has a very rapid absorption, permitting peak plasma concentration almost in 30 mins. It is uniformly distributed all over the body, including C.S.F. It crosses the placental and other barriers, quite easily.

(b) Studies with labelled INH have revealed its highest concentrations in lungs and skin and also greater penetration into caseous lung tissues and monocytes.

(c) The drug undergoes enzymatic degradation and acetylation before it is excreted in the urine, in free and broken down forms.

Anti-bacterial Activity: Of all the known drugs, INH has the highest *in vitro* activity, the bacteriostatic concentration being 0.01/ $\mu\text{g/ml}$.

It is 7 times more potent than PAS and about 4 times that of streptomycin, in *in vitro* experiments. *In vivo* also, is not inferior to streptomycin in this respect but probably even superior. The action is remarkably specific on *M. tuberculosis* and *murine leprosy* but is ineffective against other organisms.

Toxicity: (a) C.N.S. stimulation, euphoria, asthmatic attacks, hyper-reflexia.

(b) Very large doses may produce even hepatorenal damage, sometimes.

Uses: All forms of tuberculosis because of the greater facility for diffusion, and in a sense, even superior to streptomycin, though not more frequently used. Fever, toxæmia, cough, radiological findings, all improve in a few weeks and the patient feels a sense of 'well being' with increased appetite and weight. It also causes a dramatic relief in long standing cases of *lupus vulgaris*, not responding to any other form of therapy.

VIOMYCIN

As already indicated, it is derived from *Streptomyces puniceus* and is effective against various organisms, including *M. tuberculosis*. *Dose*—1 gm/day/t.d./I.M.→2 gm/week. The drug causes resistance formation and serious nephrotoxicity, deafness and allergic reactions. Its uses therefore are restricted to streptomycin resistant cases only.

CYCLOSERINE

This broad spectrum antibiotic is obtained for *Streptomyces orchidaceus*. It is water-soluble and absorbed per os. It produces gradual rising of blood level and is slowly excreted. *Dose*—0.75 gm/OS/t.d. The drug had shown promising results in renal tuberculosis but epileptiform convulsions, mental depression and psychosis are fairly common. Tetracyclines—2 gm/t.d. preventing resistance formation by antitubercular drugs, need further confirmation.

THIOSEMICARBAZONES

Though originally investigated by Domagk and observed to possess antitubercular activity *in vitro* and *in vivo*, out of these series of compounds, only *thiacetazone* or *conteben*, has been most extensively studied. Its antitubercular activity is midway between that of streptomycin and PAS but its high toxicity had precluded its use up till recent-

ly, when it was recommended for use along with INH, for the domiciliary treatment of tuberculosis, as both the drugs are used orally. It is also much less expensive for *maintenance therapy*.

PYRAZINAMIDE

A newer drug, resembling nicotinamide, which is potent but toxic for the liver. *Dose*—40 mg/kg/day/os, to a maximum of 2-3 gm/day. The drug is being used in antitubercular therapy in recent years, more frequently. *Ethionamide*: It is related to isoniazide, quite effective but gives cross resistance. *Dose*—1.5-3 gm. b.d. *Sulphone*: though effective in experimental guinea pig tuberculosis, it is not used in human tuberculosis, but used extensively in leprosy as DDS. *Triton A 20*: a surface active polyoxyethylene ether, which can suppress acute tubercular infections in mice and guinea-pigs. The drug is hepatotoxic and its newer analogue, D_2 , is comparatively less toxic. Though effective in experimental tuberculosis with fairly high cure rate, they are not much used in human therapeutics, as yet.

Nature and Mechanism of Action: This is as complex as the organism itself, involving many factors, of which, enzyme activities as well as the utilisation of metabolites, deserve special reckoning. These factors refer both to the germ as well as to the nature of drugs and are of both general and individual nature.

1. *Factors common to all drugs:* (a) *Mycobacterium tuberculosis*, which is acid and alcohol fast, has slow growth, high degree of resistance for survival under abnormal conditions of pH and environmental variations, utilising even 'glycerol' and 'asparagine', as sources of carbon and nitrogen.

(b) It uses *polysaccharides* for its necrotic action, *pthioic acid* for tubercle formation, *mycolic acid* for acid fastness and *tuberculo-proteins* for hypersensitivity reactions. The *cord factor* in young culture, is responsible for its virulence. It aptly biosynthesises a large number of essential metabolites and uses others as *substrates*.

(c) A drug inhibiting the respiratory enzyme of the organism by the blocking of the coenzymes, produces bactericidal effect, while, drugs affecting the metabolite utilisation, block cell multiplication and produces bacteriostatic action.

(d) In due course, when *cell metabolism* is so grossly altered that the synthetic work is diverted towards unnatural pathways, the resistance formation and mutation processes commence.

2. *Factors common to individual drugs:* The following are some of the important aspects in respect of the actions of individual drugs, trying to explain the mechanisms, involved in their antitubercular actions:

Streptomycin: (a) It disturbs the *monocucleotide* and RNA formation, affecting the *nucleoprotein synthesis* and *cell division*.

(b) It disturbs *polysaccharide formation*, which is an antimetabolite action.

(c) The carbohydrate metabolism and tissue respiration are affected by a block in the *Kreb's cycle*, at the stage of the *pyruvate*—oxalacetate condensation.

PAS: (a) It exerts an *antimetabolite action* vis-a-vis salicylates, pantothenic acid and PABA.

(b) The *copper chelate formation* by PAS deprives the mycobacteria of the use of trace metals, resulting in bacteriostasis.

INH: Disturbance in the pyridoxine metabolism with the blocking of the action of DPN and DPNase, by combination with nicotinamide, results in disturbed protein metabolism and B₆ deficiency.

The biochemical backgrounds of the mechanism of antitubercular action, are still incomplete and tentative and when further knowledge is obtained, it will open newer lines for understanding the specific actions of drugs not only for tuberculosis but for other fields, and also help in the synthesis of newer types of specific drugs, in the future.

PROBLEM OF DRUG RESISTANCE

At least 2 factors seem to be involved in this complex and undesirable problem of drug resistance: (a) The molecular make up of the drug and (b) The enzymatic and metabolic pattern of the germ. Though many of the links are still missing, both these factors seem to be intertwined, probably more so in this case, but also in other cases of resistance formation.

1. *Adaptive changes:* The *M. tuberculosis* is very apt to adaptive changes, permitting it to survive under almost impossible conditions:

(a) Using of short chain fatty acids, when long chain ones are blocked by streptomycin.

(b) Synthesising citric acid even in the presence of streptomycin or surviving without it.

(c) Surviving under inadequate oxygen supply. All these are due to

the adaptive changes occurring in the organism, readily and quickly, under drug therapy.

2. *Mutation*:

- (a) This is a much slower process and affects a small percentage of the *germ population*, denoting the "survival of the fittest", by a process of 'natural selection'.
- (b) It is directly proportional to the 'density of the population' and inversely to the 'size' and 'frequency' of the dose.
- (c) The 'gene pattern' of chromosome, which controls the enzyme system of the germ, is altered and thus virulence, metabolism and resistance patterns, are also changed. These characteristics are transmitted through successive generations.
- (d) Haphazard and indiscriminate use, inadequate dose and prolonged use of the drugs, are responsible for this type of pharmacological hazard, which is minimised by the 'combination therapy' and judicious use of these potent drugs but not fully eliminated.

In substance, the problem of drug resistance still remains a great enigma. The very pathology of the disease constitutes a mechanical hazard for drug action. The slow metabolism of the bacillus often renders 'drug-metabolite competition' ineffective. The hypersensitivity reaction of the host, with lack of adequate immunological responses from the drugs, excepting with the B.C.G., also subscribe to these difficulties. Specific chemical molecular blocking of the vital functions of the bacteria, without affecting the host cells, has not yet been realised and therefore complete forestalling of the resistance formation, is not possible. Accurate bacteriological diagnosis, use of specific drugs after carrying out the sensitivity test, larger dosage-schedule in acute and serious cases, intensive short term therapy in place of prolonged courses of treatment with smaller doses, and above all, *combination therapy*, particularly with INH and PAS, minimise the incidence and the degree of resistance but any ideal drug, capable of dealing with all the aspects of resistance formation, is not yet in sight.

THERAPEUTIC CONSIDERATIONS

A deadly disease and in a sense, worse than malignancy, because it cuts or cripples a man at the prime of his life. In U.S.A., alone, 1.2 million of potential life hours are lost every year from this single disease and in less developed countries, much more so.

The disease manifests itself in 2 distinct forms:

I. *Pulmonary tuberculosis*: (a) chronic fibrocaseous, (b) exudative and (c) miliary.

II. *Extrapulmonary tuberculosis*: (a) miliary generalised, (b) tubercular meningitis, (c) pleurisy, (d) bone T.B. (e) abdominal T.B. (f) tubercular adenopathy.

Formerly, good food, fresh air, cod liver oil, calcium, sanatorium treatment, gold, sulphones and vitamins, constituted the major therapeutic measures in the treatment of tuberculosis. Today, in spite of the discovery of specific drugs—streptomycin, INH and PAS and also the immunological role of BCG, the therapy of tuberculosis is not free from complexities, for reasons indicated earlier—(a) protracted course (b) inadequate bactericidal action of known drugs, (c) drug resistance and (d) inadequate defence mechanism of the host.

An *ideal* antitubercular drug should consequently be bactericidal and penetrative or bacteriostatic and relatively non-toxic for prolonged use. As none fulfils these requirements, 'combination therapy' is resorted to.

Combination therapy: A scientific approach to the planning of treatment would be based on *sensitivity tests* immediately after clinching the diagnosis. This is time consuming and not always possible, everywhere. The routine procedure, therefore, is to start treatment immediately with all the three drugs together.

- (i) Streptomycin—1 gm/day/I.M.
- (ii) I.N.H.—300 to 400 mg/day/os, in single or two doses.
- (iii) PAS—10 gm/day/os, in two divided doses.

Streptomycin is withdrawn after 4 weeks and INH and PAS continued for 12 to 18 months.

Result: According to the figures of the WHO studies; 2% relapses, as against 27% if streptomycin is not used initially and 16% relapses have been observed if streptomycin and INH are given without associating PAS in the treatment.

If the result of sensitivity tests indicate resistance of the organism to any one of the above drugs, that drug is withdrawn and replaced by one of the 'second line drugs':

- (i) Thiosemicarbazone—(100-150 mg/day), (ii) Pyrizinamide—(2-3 gm/day) (iii) Ethionamide—(1.5-3 gm/day) (iv) Cycloserine—(0.75-1 gm/day).

Thiosemicarbozone and *INH* in one or two doses/day, have recently been extensively studied and found to be relatively non toxic and effective for the domiciliary treatment of tuberculosis.

Pyrizinaide: It is a better cover for surgery, when organisms are resistant to other antitubercular drugs.

Corticosteroids—prednisolone—30 mg/day/os, under the coverage of antitubercular drugs, are sometimes used. Similarly, penicillin or broad spectrum antibiotics, protect against other infections and all these act as 'life saving', particularly in (i) T.B. meningitis and (ii) Miliary tuberculosis. Intrapleural cortisone, in massive effusions, not resolving after repeated aspirations, is also advocated.

With the advancement, already made, tuberculosis is nearly under control now and in a decade or two, it may cease to be a surgical problem and probably even a medical one, some day. This will only prove the real place and efficacy of 'specific therapies', combined with ceaseless efforts for eradication of other public health factors, in the etiology and genesis of tuberculosis.

CHEMOTHERAPY OF LEPROSY

An outstanding social stigma, which had put up a real challenge to scientific medicine, from the earliest days of our civilization. There are over 4 million cases of leprosy in the Commonwealth countries, out of which, India's share is about 1.25 million and Africa's 1.5 million. It has been practically eradicated from Scandinavian and other European countries.

The disease is as old as the modern civilization and is, also mentioned in the Old Testament, associated with the anecdotes of the miracle cures of the Lord and of the holy water of Jordan, the faith cures of Lourde and finally thermal therapy at Mangopir, in India.

The therapy thus includes everything and has been a chapter of alternating hopes and despairs, each new drug and measure, failing to substantiate the initial claims.

This obviously is due to many reasons:

(a) Difference in the two forms of leprosy, (i) *Tuberculoid form*, with few organisms, high resistance and infectivity, confined to the skin and peripheral nerve trunks, producing thickening and anaesthetic patches. Its incidence is about 30%. (ii) *Lepromatous form*, with an incidence of about 70%: no evidence of host resistance, organisms abundant, infection confined to the lymph glands, eyes and nose, causing mutilation of these organs.

(b) Inadequate knowledge of the causative agent—acid and alcohol fastness of Hansen's bacillus, its metabolic peculiarities, inadequate defence mechanism and difficulties in the induction of leprosy, excepting the murine form, which does not produce the same lesions as in human beings.

(c) Inadequate bactericidal effect of known drugs and also resistance, intolerance and toxicity hazards, inherent in such a prolonged therapy.

CLASSIFICATION

VEGETABLES	Chaulmoogra and hydnocarpus oils—their fatty acids, ethyl esters and combinations
	(a) Sulphones and their monosubstituted derivatives—DDS, promin, promacetin, promizole, diasone, sulphetrone.
CHEMICAL	(b) Thiosemicarbazone—contaben, tibione
	(c) Isonicotinic acid hydrazide
	(d) New drugs—thiambutozine, ditophal, vadrine
ANTIBIOTICS AND HORMONES	Streptomycin, ACTH and Cortisone

CHAULMOOGRA OIL

This old indigenous drug, obtained from the seeds of the *Hydnocarpus wightiana* tree, growing in Siam, Burma and Indo China. The hydnocarpus and chaulmoogra oils and their derivatives, have been in use. The active principles comprise a series of unsaturated fatty acids—chaulmoogric and hydnocarpic acids, present as glyceryl esters, which can be converted to ethylesters or sodium salts. Recently, a chemical combination of DDS and hydnocarpic acid known as *hydno-sulphone*, has been made available for use.

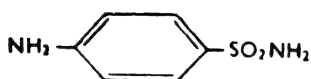
Preparation: (a) *Oleum hydnocarpii ethylicus* 1 ml, increased to 5 ml. I.M. or by local infiltration. (b) E.C.C.O. or ethyl ester of chaulmoogra, creosote, olive oil and camphor—*Dose:* 1-5 ml.

Actions and Uses: The drug was introduced by Rogers in the earlier part of the century and it has served its purposes during the past decades with mixed results. Its action is semi-specific, with stimulation of phagocytic action of the RES but there are risks of toxicity—dizziness, choking sensation, malaise, G.I. disturbances and thrombophlebitis. Its place has been taken away by D.D.S. and other newer drugs, detailed hereafter.

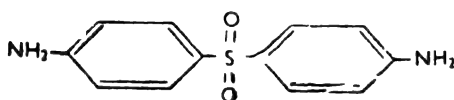
SULPHONES

These comprise diaminodiphenyl sulphone or D.D.S., promin, diasone, sulphetrone and promizole.

Chemistry: All the sulphones are derivatives of diaminodiphenyl sulphone or D.D.S., which is structurally similar to sulphonamide.



Sulfanilamide



D. D. S

Illustr. XXVII. Chemical differences in the structure of sulphonamide and diaminodiphenyl sulphone.

Metabolism: (a) The metabolism of individual sulphones is not known. They are partially hydrolysed in the intestine and then absorbed. The part which is absorbed, as such, is hydrolysed in the body to DDS, which is the active form.

(b) The sulphones are uniformly distributed in the body, excepting in C.S.F. 50% of the drug is destroyed and the rest excreted slowly in urine, tending to produce cumulation.

Action: (a) The sulphones have a bacteriostatic action on the leprosy bacilli, leading to the complete healing of the mucosal lesions. Lesions of the skin, nerve and the eyes, respond in the decreasing order.

(b) The bacteriological cure occurs in 1-3 years i.e. later than the clinical cure.

(c) Advanced and irreversible lesions, such as the pigmentation, depigmentation, scar and atrophy are not influenced by sulphones.

Diaminodiphenyl Sulphone: (a) It is the mother substance of all the sulphones which produce their antileprotic action after their biotransformation to D.D.S.

(b) Though fairly toxic, it is efficacious, cheap and readily available. The International Congress on Leprosy has accepted it as the drug of choice, displacing the use of other sulphones, in leprosy.

Dosage schedule: 25 mg/twice a week/for 2 weeks, increased by 25 mg. every 2 weeks, till 100 mg, twice a week, is given. The dose is then increased by 100 mg. monthly, until 300 mg. is given. Thereafter, 1 tab. daily/ 6 days a week. The treatment is continued for 1½-3 years. It is given in combination with vitamins B₁₂ and C.

Promin: It is a di-dextrose derivative of DDS. *Dose*—1 gm. I.V. 6 days a week, increased to 5 gm. daily after 4-6 weeks. A rest period of one week after every three weeks, is to be prescribed. *Promacetin:* 3-4 gm/ daily/per os, has also been used.

Diasone Sodium: A formaldehyde derivative of DDS, formerly used, in the form of 100 mg. tablet. *Initial dose:* 3 tabs. gradually increased to 9 tabs/day.

Promizole: It is less active than DDS but its overall toxicity is also less. *Dose*—6-8 gm/day. Its use has been restricted these days. due to its goitrogenic and gonadotrophic actions.

Sulphetrone (Solapsone): It is more effective than promin or dissone and is also much less toxic. *Dose*—6-10 gm/day/os or 1 ml. of 5% sol. I.M./twice a week; increased to 6 ml.

Toxicity: (a) Haemolytic anaemia and methaemoglobinaemia.

(b) Acute 'lepra reaction', comprising fever, erythema, malaise, neuritis, periostitis and iridocyclitis, due to massive destruction of the organism and release of toxins. The lepra reaction leaves the patients much improved and has been considered to be of special significance in therapeutics.

(c) Incidence of toxicity is very much reduced by the administration of (i) gradually increasing doses, (ii) intermittent courses (iii) iron adjuvant (iv) frequent laboratory check up of the blood (v) Use of antihistaminics, adrenaline, corticosteroids and chlorquin, in cases of severe lepra reactions.

NEWER DRUGS

Thiambutosine: It is a diphenyl thiourea compound, designated as DPT, possessing rapid action and less toxicity. It is used as an adjuvant to DDS and also in cases of intolerance to it. *Dose:* 2 gm/day.

Etussil (Ditophal): It is a diethyl dithiol isophthalate, a mercaptone derivative which releases ethyl mercaptone in the body and this is responsible for the antileprosy action. 4-5 ml. of 75% cream is applied by inunction, followed by a bath. It causes disappearance of bacilli from the skin, and enhances the value of DDS. It is, however, not a substitute for it.

Vadrine or oxydiasoline: is a derivative of P.A.S. It has rapid action and is used in patients intolerant to D.D.S.

ACTH AND CORTISONE

Also valuable adjuvants to the anti-leprotic drugs, a dose of 0.1 gm. of ACTH or cortisone, every 12 hours for 2 to 3 days, followed by smaller doses for two days, control the acute manifestations of leprosy or of sulphone sensitivity. Cortisone, 10 injections, along with hylase and vasodilators, is also used locally to reduce the fibrosis.

THERAPEUTIC CONSIDERATIONS

Amongst the newer drugs, DDS, as stated earlier, is the drug of choice. Adequate dosage, prolonged therapy and guard against toxicity, as well as resistance formation, should always be kept in view, during the period of therapy. Supportive therapy with uses of vitamins and hormones and iron, is also a necessity.

With effective treatment, clinical improvement may be obvious in 3 months or less, but bacteriological improvement is usually delayed.

In *tuberculoid leprosy*, the results of treatment are good as regards the disappearance of signs but the mutilation outcome is not affected. In the *lepromatous type*, with early diagnosis and ideal treatment, the bacterial count falls down to 50% of the original, in 6 months. Subsequent fall is delayed but with two years of therapy, the count is reduced by 75%. In 80% of the cases, the patient becomes bacteria-free, in about 4 years time.

In spite of all these, the importance of public health measures, early detection and isolation of positive cases, should not be minimised.

Babchi Oil: a fixed oil, used not for leprosy but for *leucoderma*, with depigmentation of the skin, which is wrongly considered by the lay public, to be akin to leprosy. The sterilised oil is either rubbed over the depigmented area or infiltrated intradermally, in different

areas of the affected skin. Results are not very satisfactory but its use continues for want of any better drug.

CHEMOTHERAPY OF URINARY TRACT INFECTIONS

This encompasses a group of drugs, some as relics of the past and others as advances of modern therapeutics. This is so, because, the urinary infection is complex and tenacious, affecting different parts of the urinary tract: the pelvis of the kidneys, ureters, bladder and urethra, presenting gross histological differences.

The infective agents are also of diverse nature—gram +ve, grame—ve organisms, bacilli more common than cocci; *E. coli*, gonococcus *Ps. aeruginosa*, proteus vulgaris, streptococci foecalis and haemolyticus, staphylococcus, tubercle bacilli—in the order of frequency indicated and also with differences in their sensitivity to drug actions. The incidences of mixed infections are also not uncommon.

Though some of the urinary antiseptics may be used locally for the urethra and bladder, systemic administration of a drug, which is less irritant to the mucous membrane, more concentrated in the urine and most effective against causative organisms, is by far, the best.

For *B. coli* infection, the pH factor of the urine is also important, inasmuch as, these organisms do not thrive beyond 5.5 to 8.5, easily

CLASSIFICATION

SULPHONAMIDES	Sulphadiazine, elkosin sulphatriad, gantrisin	NITROFURANES	Furadantin
ANTIBIOTICS	Streptomycin, chlor-amphenicol, tetracyclines, erythromycin.	DYES	Methylene blue, mercurochrome acriflavin
FORMALDEHYDE GROUP	Hexamine, hexyl-resorcinol	ACIDS	Mandelic acid
		VOLATINE OILS	Copaiba, sandalwood, buchu, cubeb.

Most of these drugs like sulphonamides and antibiotics, have already been studied. Their clinical status will be discussed and the remaining drugs, studied in greater detail.

HEXAMINE

Urotropine: ($C_6H_{12}N_4$): A combination of ammonia and formaldehyde, containing not less than 99% of pure hexamethylene tetramine, is a white, crystalline powder, of sweetish-bitter taste and a solubility of 1.5.

<i>Dose: Hexamine</i>	— 0.6—2 gm.
<i>Neo-urotropine</i>	— 0.5—1 gm.—less irritant and a better urinary antiseptic.
<i>Piperizine</i>	— 0.3—1 gm. acts also in (i) Uric acid diathesis, (ii) Gout, (iii) Lithiasis and (iv) Worm infection.
<i>Hexamine mandalate</i>	—A combination of hexamine and mandelic acid, is effective in <i>Pseudomona</i> , <i>E. coli</i> and <i>Staphylococcal</i> infections.

Action: Hexamine is rapidly absorbed from the G.I. tract. About 20-30% is decomposed in stomach and changed into *formaldehyde*, in acid urine, which is a powerful antiseptic. The change occurs at a pH of 6 and the urine is generally of this pH in *B. coli* infection. Otherwise, acidifying agents are to be given. It is not metabolised, but excreted in urine. As it is irritant for stomach, it is given in capsule forms.

Sometimes the urine has to be rendered *alkaline* by the administration of citrates and acetates—10 gm/day or *acidic* by acid sodium phosphate—6 gm/day, as any continuous acidity irritates the kidneys and the bladder. Ammonium chloride—0.3—1.3 gm. t.d.s. also renders the urine acidic.

Toxicity: (a) Cystitis (b) Haematuria.

Uses: The drug is very little used these days after the discovery of mandelic acid and sulphonamides, but has been used in—(a) pyelonephritis and cholecystitis, (b) Comatose conditions in septicaemia and as a (c) prophylactic agent before catheterisation. At best, it can only be tried in sulphonamide and antibiotic resistant cases.

HEXYL RESORCINOL

An urinary antiseptic which does not irritate the kidney or the bladder and its action is not dependent on the urinary pH. It is sufficiently concentrated in urine for antibacterial activity. Streptococcal foecalis, pseudomonas, *E. coli* and proteus, are the susceptible organisms for this therapy.

Uses: (a) Pyelitis, (b) Cystitis, (c) Anthelmintic for hookworm.

MANDELIC ACID

White crystals or powder, turning yellow after exposure to light; Solubility—1 in 7. Ca Mandalate is less irritant than mandelic acid itself and does not require ammonium chloride, as adjuvant, for acidifying the urine to pH 5.3. The antibacterial concentration in urine is 10^{-5} β *hydroxybutyric acid* is also an effective agent but as it is metabolised in the body and is not excreted, *Mandelate salts* are preferred. It is a substitute for ketogenic acidifiers, bringing the pH of urine to 5.3. Combined with ammonium chloride, mandelic acid acts better than when given alone. It is effective in *E. coli*, *pseudomonas* and *streptococcus foecalis* infections. If the infection is due to *pseudomonas* and *proteus* organisms, sulphonamides act better, as these organisms produce ammonia from the urea and hinder the acidification of urine. They are, however, much inferior to sulpha drugs and antibiotics. *Monoethanolamine mandalate*, a newer compound, is a better drug than mandelic acid, in this respect.

VOLATILE OILS

As already indicated in the chapters of diuretics and carminatives, a number of volatile oils also possess mild urinary antiseptic action, as general properties, during the process of their urinary excretion.

The following are the important members:

Balsam of Copaiba: an oleo-resin, obtained from the *copaifera* plants, is a viscous, aromatic liquid, soluble in alcohol. *Dose:* Oleum copaiba—0.3-1.3 ml. On oral administration, it imparts a sensation of warmth, stimulates the urinary secretion and acts as an urinary antiseptic. It is a drug which has long been used in gonorrhoea and gleet in the past but completely discarded now.

Oleum Santali: It is distilled from the dried heartwood of *Santalum album*, growing in Mysore. Pale, yellow, viscous liquid, with aromatic odour and unpleasant taste. *Oleum santali*—0.3-1 ml. It is used in—(a) Perfumery and soap industries, (b) Acute and chronic gonorrhoea with burning and cystitis, (c) Bronchiactasis with foetid sputum.

Buchu Folia: The dried leaves of *barosma*, containing volatile oil. *Dose:* 0.3-2 ml. *Infusion*—2-3 oz. *Tincture*—2-4 ml. It is a diuretic

and mild urinary antiseptic, soothing pains of cystitis, urethritis and gonorrhoea and is also a pulmonary antiseptic.

CHEMOTHERAPEUTIC AGENTS

Sulphonamides: These are of great therapeutic value and prescribed initially, in all urinary infections, excepting from *M. tuberculosis*. They are most effective against *E. Coli*, *Ps. aeruginosus*, *salmonella* and shigella group of organisms. *Daily dose:* 2-4 gm. in divided doses, supplemented by adequate fluid therapy and sodium bicarbonate for the alkalisiation of urine.

Elkosin: (sulphisomidine), *sulphadiazine*, *sulphadimidine* and *sulphafurazol*, already dealt with in the chapter of sulphonamides, are the commonly used ones, because of their higher urinary concentration and greater solubility of the acetylated form.

Furadantin: A nitrofurane derivative, used in refractory urinary tract infections. It has a broad spectrum of activity and is concentrated in acid urine. Its antibacterial activity is due to its ability to act as an electron acceptor for reduced flavoproteins. It is well tolerated, having few side-effects excepting nausea and vomiting. *Dose:* 5-8 mg/kg/day, in divided doses. It is mainly indicated in G.U. infections, due to *E. coli*, *proteus vulgaris* and *streptococcus faecalis*. It produces less resistance than others and is often kept as a reserve for tenacious cases, when other drugs fail or the organism becomes resistant to them.

ANTIBIOTICS

Penicillin: A narrow spectrum antibiotic, which is only of value in urinary tract infections, caused by staphylo, strepto and gonococcal infections. It is of no value in gram -ve bacillary infections.

Streptomycin: Another narrow spectrum antibiotic, useful in acute and chronic urinary tract infections but due to high incidences of drug resistance and the risk of damage to the VIII nerve, it is only used in tubercular infections of the urinary tract. *Dose:* 1.5 to 2 gm/day, I.M. divided in two doses. for 5-7 days, along with 2 gm. of sodium bicarbonate/4 hourly.

Chloramphenicol: This broad spectrum antibiotic is used in gram -ve acute, or chronic infections. It is more effective against bacilli than cocci. *Daily dose:* 2-3 gm. till the urine culture becomes negative.

It is also used *prophylactically* and post-operatively, in urogenital surgery. However, due to the dangerous risk of its causing *agranulocytosis*, and bonemarrow depression, its use is reserved for enteric fever only, in which, a very short course of therapy is needed and there is no other better drug than this.

Tetracyclines: Broad spectrum antibiotics, comprising aureomycin, aëchromycin, terramycin and demethylchortetracyclines, are effective against a large number of organisms and routinely used in the therapy of urinary tract infections, as well as, prophylactically, prior to surgical interventions and in refractory cases. *Dose:* Ledermycin—1-2 gm. daily, for 5-7 days, along with vitamin B. complex, constituting a course of treatment. It can be combined with other drugs as well, if needed.

CLINICAL STATUS

Urinary tract infections are extremely tenacious and often bafflingly unyielding to all forms of therapies, because of the diversity of organism, which are usually of varying nature, unequal drug sensitivity, easily prone to resistance formation and increasing incidences of drug sensitisation, during the course of a prolonged therapy.

While the majority of cases may yield to single or combination therapies of sulphonamides and antibiotics—elkosin, furadantin, tetracycline, and occasionally, chloramphenicol, streptomycin and rarely, penicillin, polymixin and neomycin, there are cases, in which, all these measures fail and even older drugs like hexamine, mandelic acid and auto-vaccine therapies, have to be tried, one after another, over prolonged periods, to make the patient infection-free. The chances of relapses or recrudescences, being fairly common, the patient has to be under observation, over long periods, with regular laboratory check ups of urine. In *acute condition*, rest in bed, 4-5 pints of fluid/day, Na citrate and bicarbonate—2 gm. each/4 hrs, are also to be prescribed.

Drug therapy: For different organisms, comprises the following:

(a) *E. coli infection:* This is most frequent and amenable to *Elkosin* (sulphasomidine): 2 gm—1 gm. t.d.s. and, if necessary, *Furadantin*: 7.5 mg/kg/day, in divided doses, for 2-4 weeks. Sometimes *tetracyclines* and *gantrysin*, are also used.

(b) *Proteus vulgaris:* *Ampicillin*: 2-4 mg/day and/or *Chloramphenicol*—0.5 gm/6 hrs. for 7-10 days. For *other species*—*chloramphenicol*, *gentamycin* and *kanamycin*, may have to be used.

(c) *Ps. aeruginosa*: Colistin—5 mg/kg/day, in divided doses and also polymixin B—2.5 mg/kg. I.M. per day, gentamycin and tetracyclines, are indicated.

(d) *Streptococcus faecalis*: Sulpha drugs and furadantin, may be tried.

Staphylococcus and streptococcus haemolyticus: Erythromycin and procain-penicillin—6 lac units/day;

(e) *Gonococcus*—penicillin only and in *T.B. infection*—streptomycin, should be used.

With all these new drugs, along with the surgical handling of the underlying causes of persistent infection, the prospect of control and cure of U.T. infection has no doubt undergone radical changes, but it should still be remembered that as in the cases of tuberculosis and leprosy, it offers a terrain, in which, the physician's skill and patience, are no less put to a challenge by the invading organism, known for its notoriety in course and character, baffling the known drugs from effecting any cure of a radical nature, easily.

CHAPTER

48

CHEMOTHERAPY OF MALIGNANCY OF BLOOD AND OTHER TISSUES

GENERAL CONSIDERATIONS OF NORMAL AND ABNORMAL CELLULAR PROLIFERATION. DRUGS ACTING ON THE MALIGNANCY OF BLOOD AND OTHER TISSUES. THEIR MECHANISMS OF ACTION AND CLINICAL STATUS

[With the conquest of infectious diseases and better control of child mortality, expectancy of life has very much increased. Consequently, geriatric diseases and incidences of malignancy have also assumed much greater importance, the latter becoming almost the second biggest killer of human lives, in modern societies.

Though phenomenal advances have been made in the field of cellular pathology and mode of study of cancer cells and a number of effective drugs, acting through the metabolic pathways, affecting the proliferation of cells, in respect of blood and other tissue cancers, have been discovered, the therapy is still of a palliative nature excluding many other forms of cancer, which are still much beyond the scope of modern therapeutics.

Drugs used in blood and other malignancies belong to the groups of (a) *Alkylating agents*—ethyleneimine derivatives and radiomimetic substances; (b) *Antimetabolites*—purine and folic acid antagonists, hormones, and radioisotopes and (c) *Antibiotics*—actinomycin, neomycin, Dox, azaserine.

Clinically, for *acute leukaemias*—aminopterin, 6 mercaptopurine, corticoids and urethane are used; for *chronic leukaemias*—myleran, nitrogen mustard, radio phosphorus, TEM and ACTH; for *Hodgkin's disease*—nitrogen mustard, actinomycin; for *prostate cancer*—oestrogen and radio active gold; for *breast cancer*—oestrogen and androgen; for *thyroid cancer*—radio active iodine and for *polycythaemia vera*—radio active phosphorus and acetyl phenylhydrazine, are in use.]

Introduction: Modern medicine has spared mankind from the afflictions of infective diseases, which sometime ago, would have been fatal. The longevity of man has been increased amazingly fast. Under the pleasing realisation of industrial affluence, accompanied by inevitable atmospheric pollution and increasing exposure of man to drugs and chemical influences, the new hazard of increasing cancer incidences has placed it on the pedestal, as the second biggest killer of human lives.

In spite of rapid advances in most of the branches of medicine, drug treatment of cancer still remains, at best, rudimentary and palliative. The reason for this is our lack of understanding of the specific biochemical defect, which results in the wanton proliferation of cells, causing cancer. Fortunately, the concerted efforts of biological scientists with modern techniques of histochemistry and electron microscopy, have started unravelling the normal biochemical composition of living cells and attempts are being made to find out not only the mechanisms which result in their orderly multiplication into exactly similar daughter cells, but also the derangement which accelerates this process, leading to the formation of functionally useless cancer cells, which are so different from the normal ones and so undifferentiated, that even the *immune mechanism* of the body fails to check their indiscriminate proliferation and invasiveness. The crucial point still awaiting further elucidation is some biological mechanism which would be existing in cancer cells and not in normal ones, so that by attacking that, with a drug, a *specific selective lethal action* on the cancer cells, can be produced without harming the normal ones.

Biochemical Considerations: A normal cell consists of *nucleus* and *cytoplasm* enclosed in the *cell membrane*. The identity of the cell and its characteristics are coded in the *chromatin network* of the nucleus, more specifically in a substance known as *desoxyribonucleic acid* (DNA). The nucleus is the most important structure which initiates cell division through a series of stages *prophase*, *metaphase*, *anaphase*, *telophase*, and *interphase* through its various substructures, like *microsomes* and *mitochondria*. The *cytoplasm* performs intricate chemical synthesis and degradation reactions, which help the cells to grow and remain functioning efficiently. The process of synthesis of proteins and thereby, of vital enzymes, takes place in the *ribosomes*. The exact proteins to be formed are determined again by the nuclear D.N.A., which sends the requisite information through a messenger substance, known as *ribonucleic acid* (R.N.A.), a substance abundantly present in the nuclei, as well as in the cytoplasm, where it helps to bring the activated amino-acids to the ribosomes for protein synthesis.

Drug Action: The anti-cancer drugs, known so far, affect some of the above biochemical steps and cause either an arrest of the cell division or cell growth by depriving them of their *essential metabolites*. Others destroy the cells by *ionisation*, which results in the activation of the various enzymes and the active chemical radicals.

A drug acting on the cancer cells also causes a *lethal effect* on the

normal cells. However, in most cases, due to their rapid metabolic turnover, a larger quantity of drug reaches them. This results in the greater destruction of cancer cells, as compared to the normal ones. At the same time, a very slight increase in the dose of these drugs results in widespread death of normal tissues. Thus the *therapeutic index* of anticancer drugs is very slow.

Any drug capable of affecting cell function in such a profound manner, so as to kill it, can in sublethal concentrations, modify cells without killing them. This results in developmental anomalies in the embryos, an effect denoted as *teratogenic*.

A very important action exhibited by anticancer drugs is the ability of the *reticuloendothelial* cells to reject foreign material, introduced into the body. Obviously, this happens from the specific destruction of such cells, in the reticuloendothelial system, which confer *immunity* to the body, against foreign substances. This property is useful in situations like grafting of organs from one person to another, dealt with in Chapter 50.

Mode of Study: One of the main reasons for slow progress in the chemotherapy of malignancy is the inadequacy of any test systems which presupposes the following essential prerequisites:

- (a) Discovery of suitable carcinogens for experimental carcinogenesis in animals.
- (b) Discovery of an accurate test method for screening and evaluation of anticancer compounds.

Our knowledge in respect of both, though better than in the past, is still grossly deficient.

Carcinogens: These are substances, which by causing deleterious effects on normal tissues, induce them to function like the unmeaningfully proliferating cancer cells, in the body. Many irritating substances like benzene, gasoline, tobacco, betel nut, tar derivatives, X-rays, radium etc. have been assigned to possess carcinogenic properties, as a result of group studies. Broadly speaking, they can be categorized as:

- (a) Drugs and chemicals.
- (b) Physical agents.
- (c) Viruses.

All these agents are of so diverse nature and possessing such varying degrees of carcinogenic properties that it is not easy to assess their

exact pathogenesis correctly, with due elimination of probable fallacies. The most important group, however, seems to owe this activity to its containing some carcinogenic hydrocarbons, which are polycyclic compounds of:

- (a) Benzanthracin, dibenzfluoren and dibenzacridine derivatives
- (b) Azo-dyes
- (c) Steroids and (d) Pyrolidine alkaloids

Experimental carcinogenesis: or induction of cancer in laboratory animals with any of these agents, is beset with many difficulties. The important study procedures, at present followed, are:

- (a) Transplantation of solid tumours in animals
- (b) Tissue culture technique in embryonated eggs
- (c) Cyto-pathological studies

None of these study systems, however, has been suitable enough for study of different types of human neoplasms. Of all of them, the solid tumours have been much more extensively used than others, though not without limitations, referred above.

Screening of prospective anticancer agents, is carried out by any or more of the above test systems. Of these, *Crocker Sarcoma-180*, in mice, is more often used than others. *Tissue Culture techniques* are much less cumbersome, simpler and easier for manipulation, with much less amount of materials. *Cyto-histopathological* assessment of drug effect, as a guide to the clinical evaluation of drug therapy, in disease processes, is also carried out, as a routine measure.

As stated earlier, none of these systems is fully satisfactory, so far as human cancers are concerned. Some of these tumours are susceptible to one type of chemical agents than others and are useful in detecting anticancer activity in these types only, while others are not. No one test system is therefore available which is adequately sensitive to all the compounds and also active against different types of human neoplasms.

Drug therapy of malignancy is of recent origin and has just started making some break throughs. The results are encouraging in certain forms of blood and tissue cancers, but disappointing in others. The reasons for this are inherent in unsatisfactory screening methods, for experimental studies, and also consequent deficiencies in drug-designing, due to inadequate knowledge of cancer pathology itself. However, with the drugs already available, regression and palliation

of disease processes and prolongation of life, are possible, in a number of cases, and when the present limitations of insufficient specificity of action, toxicity and resistance formation, are eliminated by the designing of better drugs, the position will further improve.

With this background of general considerations, it is proposed to study the chemotherapy of malignancy, which comprises two important groups of conditions.

I. CANCER OF BLOOD TISSUES

II. CANCER OF OTHER TISSUES

The *first* refers to the study of blood malignancies of W.B.C. and R.B.C. components and comprises drugs used in the therapy of different types of leukaemias and also polycythaemia vera, referred earlier. The *second* refers to other tissue malignancies, such as Hodgkin's disease, myeloma, lymphosarcoma, uterina, breast, prostate and other cancers, detailed hereafter.

The drugs used for both these groups of conditions being virtually the same, their classification, distinguishing features, modes of action and toxicities will be studied together and then their scopes of therapeutic uses, in the two types of cancers, separately dealt with.

CLASSIFICATION OF DRUGS

ALKYLATING AGENTS

P-chlorethyl derivatives:

Nitrogen mustard.
Leukeran (chlorambucil).
Cyclophosphamide (Endoxan).

Ethyleneimine derivatives:

T. E. M. (triethylene melamine).
TEPA.
Thio-TEPA.
Myleran and half myleran.

RADIOMIMETIC SUBSTANCES

Urethane.
Demecolcine.
Colchicine.

PHYSICAL AGENTS

X-ray, Radium.
Radioactive I, Au, Chr, P.

ANTIMETABOLITES

Purine analogues:

6-mercapurine analogue.
2-6-diaminopurine.
6-chlorapurine.

Folic acid analogues:

Aminopterin.
Methopterin.

HORMONES

ACTH and Cortisone, Prednisone, Oestrogens, Testosterone, Androgens, Progestrone.

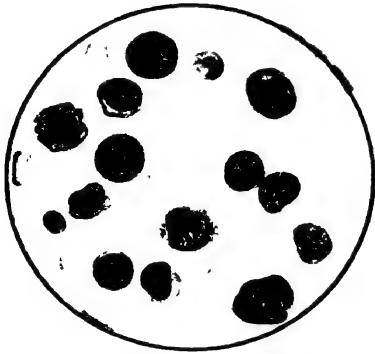
ANTIBIOTICS

Azaserine, DON, mitomycine, Dactinomycine.

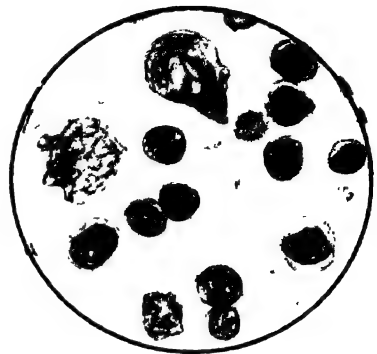
MISC. AGENTS

Vinblastine and Vincristine
1-asparaginase, Procarbazine
Mepacrine.

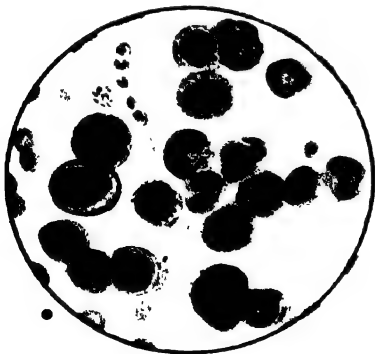
Plate XLI



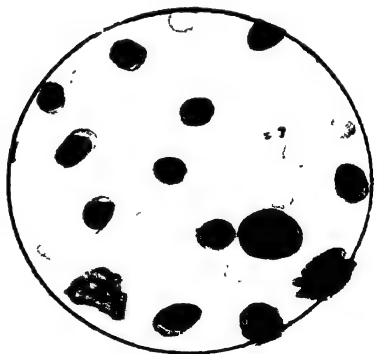
(a) Acute Myeloid Leukemia



(b) Acute Lymphatic Leukaemia



(c) Chronic Myeloid Leukaemia



(d) Chronic Lymphatic Leukaemia

Fig. 110. Blood picture in different types of Leukaemia.

General Modes of Action: These drugs act by diverse mechanisms, ultimately disturbing the cell metabolism and proliferation. The *alkylating agents* of the type of nitrogen mustard, cyclophosphamide, chlorambucil, act by virtue of their *alkyl group*, linking with the large DNA molecule, disturbing its folding and unfolding and thus eventually affecting protein synthesis in the ribosome. Their effects are qualitatively similar to those of radiation. For this reason, they have been called *radiomimetic*. In this manner, cancer cell metabolism is disturbed and even lethal mutants formed. If a tumour shows resistance to one, it usually is resistant to others in this group, as well.

The group of *antimetabolites* disturbs the formation and utilization of essential metabolites which are required for viability of the cell. They may act by : (a) competitive interference with a normal substrate (b) incorporation into a molecule producing an abnormal substance or (c) by binding an enzyme and blocking the important functions of the cell. They are closely resembling analogues and consequently, the cell cannot discriminate between the two and this may even result in lethal synthesis. *Methotrexate* is a typical example of this.

The *natural substances* like *vinblastine* and *vincristine*, probably arrest cell division in the *metaphase*, by impairing *spindle formation*. They are closely related in structure but having different spectrum of activity and toxicity. *Vinblastine* has its value in the treatment of systemic Hodgkin's disease and lymphosarcoma, in patients, who fail to respond to alkylating agents. *Colchicine* arrests cell mitosis. Interference with glutamic acid metabolism in the citric acid cycle and its counteraction by the administration of glutamic acid has been observed in these cases.

Actinomycin D or *Dactinomycin* and *Levo-asparaginase* may combine with guanine moiety in the D.N.A. helix, inhibiting the formation of messenger RNA, thus resulting in the suppression of protein synthesis. *Actinomycin D* sensitises the tissues to X-ray radiation. *Levo-asparaginase* disturbs the synthesis of amino acid asparagine and produces its action.

Procarbazine has sometimes been used in the treatment of advanced Hodgkin's disease and quinacrine, in the control of malignant pleural, pericardial and abdominal effusions. They do not depress bone marrow and can be used concomitantly with the cytotoxic drugs. There is no cross-resistance between procarbazine, vinblastine and the alkylating agents and thus it is used in patients who are refractory to these agents and also in combination therapy.

The *hormones* of the type of glucocorticoids, androgens and progestins have a large number of actions in the control of proliferation

and function of tissues, including mammary and prostrate glands. Cancers of these tissues may be produced by disturbances in their *homoeostasis* which can be inhibited by appropriate changes in the hormonal balance. They also work in combination with other cytotoxic drugs, and after ablation of some of those endocrine organs. The *radioactive isotopes* act on the basis of their ionizing effects, which lead to tissue lethality.

General Toxicities: All these drugs, however, are more or less toxic and the tragedy is that their effective dose is quite close to the toxic level.

- (a) Bone marrow depression, leuco and thrombocytopaenia, nausea, vomiting, diarrhoea and other gastro-intestinal disturbances; depression of spermatogenesis; skin and hair troubles, including alopecia; foetal death and teratogenicity, are some of the general toxic effects, varying from one individual to another.
- (b) Prolonged uses of androgens and oestrogens produce masculinization and feminization effects, with uterine bleeding. Adrenocorticoids may give rise to hypertension, diabetes and increased susceptibility to infections.
- (c) Toxic effects of vincristine are—areflexia, peripheral neuritis and paralytic ileus and that of L-asparaginase—fever, chills, nausea liver dysfunction, mental depression, reduced level of certain serum proteins, acute pancreatitis and sometimes anaphylactic shock.

Notwithstanding these toxicities and narrow safety-margins, the cytotoxic agents find frequent uses in the malignancy of blood and other tissues, with results varying from dramatic relief to inefficiency.

Regression is frequent, remission can often be expected but relapses are also common. The courses of diseases can often be modified and expectation of life prolonged. Even such palliations have their value in these dreadful conditions, with irrevocable courses and fatal end-results.

URETHANE

Though *ethyl carbamate* has long been used as a sedative and hypnotic, its cytotoxic activity has been discovered only during the last decade.

Action: (a) Though a cumulative drug, it is satisfactorily absorbed through the G.I. tract and slowly metabolised in the body. (b) It is an

important cytotoxic agent interfering with cell division in the germinal tissue of bones, thus affecting the proliferation of abnormal leucocytes. The action is probably mediated through some disturbance in the biosynthesis of nucleic acid.

Uses: 1-4 mg/day in enteric coated capsule or elixir—25% 4 ml. diluted in water. It is used in chronic myeloid and granulocytic leukaemias. It has also been extensively studied in the therapy of multiple myeloma but due to its gastro-intestinal toxicity, from high oral doses, it is much less frequently used these days.

NITROGEN MUSTARD (MECHLORETHAMINE)

These are nitrogen analogues of B-chlorethyl amino derivatives of the vesicant mustard gas, used for chemical warfares and studied during World War II. *Dose:* 0.2 mg/kg; 10 mg/ml—a low I.V. drip, daily, for 4 days.

Actions: (a) It has a marked cytotoxic effect from cellular enzyme inhibition on proliferative cells, with selective affinity for liver, lymph nodes, spleen, bone marrow and G.I. tract.

(b) It depresses both lymphoid, as well as, bone marrow tissues, leading to aplasia, in high doses.

Toxicity: (a) Marked G.I. upset and muscular weakness; lympho-granulocytopenia and thrombocytopenia.

(b) Moderate anaemia and also vascular collapse and respiratory failure. The haemalopoietic depression is minimised by the lowering of pH of the solution and by concomittant use of adrenaline. Skin eruptions and herpes zoster are occasionally observed during the therapy. Menstrual irregularities, as well as, foetal abnormalities in animals, have also been found.

Uses: *Theoretically* in (a) Chronic leukaemias, (b) Hodgkin's disease and (c) Bronchogenic carcinoma, but *in practice*, due to the toxicity, it is seldom used, excepting sometimes in *Hodgkin's disease*, when other measures fail. The therapy is purely palliative.

AMINOPTERIN

4-amino folic acid, is a *folic acid antagonist*, inhibiting the neoplastic growth in experimental sarcoma and other animal neoplasms. It causes definite remissions in *acute leukaemias*, children responding

better than the adults. *Dose:* 0.5-2 mg/daily I.M. It however causes ulcerative stomatitis, anorexia, abdominal pain and diarrhoea.

METHOPTERIN

A 10-methyl folic acid derivative and chemically related to aminopterin. It is less toxic and is used in *acute leukaemia in children*. *Dose:* 2.5-5 mg/daily.

Of late, *amethopterin* or *methotrexate* is being currently used in its place, in *acute leukaemias*, chorionic carcinoma and also, with less beneficial results, in breast cancer. It is an established *immunosuppressive* agent. *Dose:* 2.5-5 mg. in *children* and 2.5-10 mg. for *adults*. A course lasts for *three weeks*.

TRIETHYL MELAMINE (TEM)

It is transformed into ethyleneimine rings in the body and like nitrogen mustard, shows active cytotoxic effect and also, the same type of toxicity. It is recommended in *leukaemias*, Hodgkin's disease and other malignant conditions. The therapeutic indications are thus similar to nitrogen mustard. This also applies to *thiotepa* or triethylene thiophosphoramidate. *Dose:* 0.1-0.3 mg/kg, in the form of 5 mg. *tablets/day* I.V. *Dose:* 0.05 mg/kg.

LEUKERAN

Also known as chlorambucil, it is a derivative of nitrogen mustard and closely resembles it in pharmacological actions and therapeutic uses. It is much less toxic and is a safer drug for *leukaemias* than its parent compound, nitrogen mustard. It is the slowest acting and safest nitrogen mustard in chronic lymphocytic *leukaemia* and is the drug of choice. *Dose:* 4-10 mg. *os/day*, for 3-6 weeks, in the form of 2 mg. sugar coated tablets. The dose is to be modified according to the blood picture. *Initial daily dose* is 0.1 to 0.2 mg/kg of body weight, continued for at least 3-6 weeks. On clinical improvement, the dose is reduced. The *maintenance dose* is 2 mg. daily.

PURINETHOL (6-MERCAPTOPURINE)

An analogue of adenine and hypoxanthine, it interferes with nucleic acid synthesis and is effective in *acute myeloid leukaemias*, more than the *chronic ones* and other malignant conditions. It also acts and is used

as an *immunosuppressive agent*. Dose: 100-200 mg./os/day, for *adults*, and 50 mg., daily, for *children*. If there is no response in 4 weeks, the dose may be doubled or increased to the point of evidence. The average *daily oral dose* is 2.5 mg/kg, usually given as a singly, diminished gradually to the *maintenance dose*, which is an appropriate multiple of 25 mg. Its *toxic effects* are—bone marrow and G.I. tract depression.

AZASERINE

An antibiotic, obtained from *Streptomyces fragilis*, having antineoplastic activity. It is a crystalline, water soluble powder of proven value in combination therapy with *purinethol*. It is used, in a *dose* of 2.5 mg/per kg. It produces glossitis in a certain percentage of cases. The drug has also important *immunosuppressive* actions and is used in organ transplantation procedures. It is, however, a very expensive drug.

BUSULFAN (MYLERAN)

A sulphonic acid ester, which is a white crystalline, tasteless, insoluble powder. It depresses myelopoieses of immature granulocytes and also platelet formation. It is used in myelocytic leukaemia and polycythemia vera. It is effective even in those cases which do not respond to the radiation therapy. It is of no value in acute leukaemia. It is available as 2 mg. *tablet*. Initial oral dose varies from 4-12 mg, according to severity of condition and adjusted to a maintenance therapy of 1-3 mg per day. Its *toxic effects* include—nausea, vomiting, diarrhoea, sterility amenorrhoea and foetal abnormalities.

A.C.T.H. AND PREDNISOLONE

These new drugs, already studied in the Chapter of hormones, have established some therapeutic role in *acute leukaemias* of both lymphatic and myeloid varieties, in *children*. They produce dramatic responses in about 50-70% cases.

Their mechanism of action is still ill-understood. They have lytic effects on the lymphocytes and eosinophils and prevent cellular proliferation. This action is purely palliative and high doses may produce hypercorticism—Cushing syndrome and oedema.

Other Drugs: COLCHICINE stops mitosis at the stage of metaphase. DEMECOLCHICINE, a desacetylamethyl colchicine, is used for the study.

of chromosome and the rate of mitotic activity. It is not used in malignancy due to the availability of other safer and more effective drugs. VINBLASTINE and VINCRISTINE (Oncovin) are alkaloids of VINCAROSEA, destroy mitotic spindle and arrest mitosis at the metaphase. VINBLASTINE is used in resistant cases of Hodgkin's disease, neuroblastoma, carcinoma of breast, lymphosarcoma. It may cause G.I. upset, bone-marrow depression, and alopecia, indicated earlier. VINCRISTINE is used in acute leukaemia along with prednisone and also in lymphoma, in children. Its neurotoxicity—areflexia and neuritis, limits its use. DACTINOMYCIN is effective in Wilm's tumour and sarcomas. It is toxic and may produce ulcerative stomatitis, skin rashes, nausea, and vomiting, bone-marrow depression. L-ASPARGINASE, an enzyme from *E. COLI*, it deprives malignant cells of the essential asparagine. Its efficacy in malignancy is still being evaluated. PROCARBAZINE is a derivative of hydrazine and produces remission in Hodgkin's disease. It is toxic for G.I.T. bone-marrow and C.N.S. DON (6-diazo-5-oxo-1-norleucine) is a glutamine antagonist. It interferes with purine synthesis by inhibiting the conversion of formalglycinamide ribotide to formalglycinamide. Though found to be effective in animal screening, because of its toxicity, it is not used clinically. MITOMYCIN-C isolated from *Streptomyces caespitosus*, has been found to possess anticancer property by disturbing D.N.A. synthesis. Though effective and initially used in doses of 1 mg/kg. body weight, in lymphomas, chronic leukaemia and other solid tumours, because of its bone marrow toxicity, weight loss and intestinal paralysis, it is not used therapeutically.

CLINICAL INDEX—MALIGNANCY OF BLOOD : (Plate—XLI, Fig. 110)

ACUTE:	<i>Myeloid</i>	6-M.P., Thioguanine, Prednisone, Vincristine, Aminopterin.
	<i>Lymphocytic</i>	Vincristine, Prednisone, Methotrexate, Endoxan, L-asparaginase.
CHRONIC:	<i>Myeloid</i>	X-ray, P ³² , Myleran, TEM ₁ , Thio-TEPA, Urethane,
	<i>Lymphocytic</i>	X-ray, P ³² , ACTH, Thio-TEPA, Myleran, Nitrogen Mustard.
MONOCYTIC :	<i>Acute</i>	6-M.P., Aminopterin, ACTH, Prednisone.
	<i>Chronic</i>	X-ray. TEM.
MYELOCYTIC:		Busulfan (Myleran), Allopurinol 6-M.P.
POLYCYTHAEMIA VERA:		P ³² , Phenylhydrazine HCl, Blood letting.

CLINICAL INDEX—OTHER TISSUE MALIGNANCIES

HODGKIN'S DISEASE

Mechlorethamine, chlorambucil, vinblastine, prednisone, TEM, Thio-TEPA.

MULTIPLE MYELOMA

Alkylating agents—cyclophosphamide, corticosteroids, gamma globulin, X-ray.

ENDOMETRIAL CARCINOMA

Progesterone, hydroxy progesteron capionate.

PROSTATE CANCER

Oestrogens, prednisone.

BRONCHOGENIC CARCINOMA

X-ray, mechlorethamine, Endoxan.

MALIGNANT EFFUSIONS

Fluid removal, instillation of radiogold, chromium and atabrine solutions.

LYMPHOSARCOMA & RETICULO CELL SARCOMA

Alkylating agents — cyclophosphamide mechlorethamine, TEM Prednisone, vinblastine, vincristine, endoxan, Thio-TEPA, chlorambucil.

BREAST CANCER

Testosterone propionate, diethylstilbesterol, 5-fluorouracil, cyclophosphamide, vincristine, vinblastine, methotrexate.

CHRONIC CARCINOMA OF UTERUS

Methotrexate.

OVARIAN CARCINOMA

Chlorambucil, Endoxan, Mechlorethamine, TEM, Thio-TEPA.

G. I. T. CARCINOMA

Fluorouracil.

THERAPEUTIC DETAILS

As indicated, the incidence of malignancy, all over the world, is high and is probably, next only to cardiac diseases. Of the 8 *common types* of cancers, those of lungs, rectum, breast, uterus, prostate, kidney, lymphoma and blood, constitute over 70% of incidence, with about 70% of overall fatalities. Advanced scopes for early detection, improved operative techniques, more accurate radiotherapeutic measures and also the newly discovered chemotherapeutic agents of the last few decades, have, no doubt, made important breakthrough, changing the prognosis of several forms of blood and tissue cancers, but for reasons stated earlier, true specifics, affecting cancer and not host cells, have not yet been found out, for most of the cases.

Current therapy of malignancy of blood and other tissues, depends on the nature of the malady and its severity.

For *Acute Lymphocytic Leukaemia of children*, the practice is to use a combination of *vincristine* and *prednisone* for initial induction of remission and with this, over 85% of children undergo complete regression with minimal toxicity. As a *maintenance therapy*, metho-

textrate, *endoxan*, *L-asparaginase* and *daunomycin* are used. In chronic condition, X-ray therapy, P^{32} , TEM and nitrogen mustard are considered.

In *adult acute myeloid leukaemia*—the drugs of choice are: 6-mercaptopurine, thioguanine, prednisone and vincristine and in *children*—aminopterin. For *myelocytic leukaemia*—Busulfan (Myleran), 4 mg/day/O.S., initially and 2 mg. thereafter, is used. *Allopurinol* sometimes acts as prophylactic. In cases of *resistance*, *mercaptopurine* is used. Expectancy of life is increased from 3-5 years.

In *Hodgkin's Disease*, besides super-voltage X-ray therapy, in *acute state*, *mechlorethamine*, 0.4 mg/kg. I.V., followed by a maintenance therapy with *chlorambucil*, *vinblastine* or *procarbazine*, is advocated. *Prednisone* also is used for acute hemolytic anaemic state.

Regarding *Lymphosarcoma* and *Reticulo-cell Sarcoma*, the former responds better to chemotherapy, besides radiations. The *alkylating agents*, vincristine and prednisone, *mechlorethamine*, *endoxan* and *chlorambucil*, are mostly indicated. *Vincristine*, in a dose of 0.012 mg/kg., is specially suited for the induction of remission and prednisone, as supportive therapy.

For *Multiple Myeloma*—with *alkylating agents* and *corticosteroids*, definite improvement occurs in about 30% cases. The therapy has to continue for 3-6 months and expectation of life is increased from 3-4 years. Gamma globulin and X-ray therapy, improve bone pain.

For *Breast Cancer*, hormone therapy is indicated in disseminated conditions, mostly. The result is of an average type and of palliative nature.

(a) *Androgens* of the type of testosterone propionate, may be used in both pre- and post-menopausal cases. The treatment has to continue for months and improvement occurs in 25% cases only. It relieves bone pain but causes virilism, hirsutism and hypercalcaemia, to be treated by prednisone and reduction of calcium intake, (b) *Oestrogen-therapy* can be used for both the sexes but in *female*, not before 5 years of menopause. It makes them worse if used in the premenopausal period. *Diethylstilbesterol* is mostly used and some relief can be expected between 1-3 months of therapy. It does not have any effect on bone metastasis but causes sodium retention, oedema, anorexia, pigmentation, uterine bleeding and sometimes even exaggeration of growth, (c) *Adrenocorticoids*—cortisone and prednisone, often produce a subjective improvement without any regression of the tumour. They sometimes improve cerebral metastasis and anaemia, (d) Of the *non-hormonal chemotherapeutic agents*, *5-Fluorouracil*, in refractory cases, is used. It is effective in 30% cases, in doses of 75 mg/kg I.V.

for about 6 months. *Cyclophosphamide*, *vincristine* and *methotrexate* also show some activity. In substance, management of *breast cancer* involves the use of (i) Hormone (ii) 5-Fluorouracil and (iii) Alkylating agents.

Endometrial Carcinoma—*Progesterone* produces dramatic regression in 25% cases, while hydroxy-progesterone caproate is much less effective in this condition.

Chorionic Carcinoma of Uterus—arising from the foetal trophoblasts, is dramatically improved with massive doses of 25 mg/day for 4-5 days of *methotrexate*. The drug produces permanent regression in a high percentage of cases, including metastasis.

Prostate Cancer—Oestrogens and prednisone therapy produces considerable improvement in about 80% of cases and expectation of life, even without surgery, has very much increased.

For *Ovarian Carcinoma*—*chlorambucil*, *endoxan* and *mechlorethamine*, are of some value but the improvement does not last for more than a few months.

Bronchogenic Carcinoma—Besides palliative X-ray therapy, *mechlorethamine* and *endoxan*, are mostly used but the result, on the whole, is unsatisfactory.

For *G.I.T. Carcinoma*—5-Fluorouracil, 15 mg/kg., offers temporary improvement in adenocarcinoma of colon but it is toxic for the digestive tract, causing stomatitis and ulceration.

For *Malignant Effusions*, in serious cavities, after removal of effusion fluid, fresh solutions of radioactive gold and chromium phosphate and atebine, are instilled and the position of the patient changed, in a manner, that the solution comes in contact with the surface of the cavity.

The above account however encouraging, does not make one oblivious of the task ahead before the problem can be satisfactorily resolved. This refers to (a) better knowledge of cancer pathogenesis and (b) designing of chemotherapeutic drugs, in a *made to order* manner, as specific therapeutic agents, for correcting the abnormal tissue proliferation. The present efforts seem to be on the right direction and it is likely that medical research skill will be able to accept the challenge for newer and better discoveries, in the near future.

Assuming that this is possible in a reasonable period of time, newer ones will arise as is always the case in all scientific advancements—while the world of the known enlarges, the universe of the unknown, unfolds itself with newer aspects of study. That is why science can never attain any absolute finality. Its progress continues.

CHAPTER

49

PHARMACOLOGY OF LOCAL ANTISEPTICS AND DISINFECTANTS

DEFINITION AND SCOPE. DIFFERENCES WITH SYSTEMIC ANTI-INFECTIONAL DRUGS. ANTISEPTICS WITH GENERAL AND SPECIAL ACTIONS. MODE OF ACTION, STATUS AND LIMITATIONS

[A counterpart of systemic anti-infective chemotherapeutic and antibiotic drugs, which may act as general or special dis-infecting agents, depending on their nature of action and purpose of use. When used for tissue antiseptics, the effect is more often bacteriostatic than bactericidal, which latter, if not of a very special nature, may disturb the natural tissue defence-mechanism, as in the case of the disinfectants.]

The antiseptics, acting locally, belong to widely different groups—the soaps and detergents, metallic salts, phenols, oxidising agents, alcohol, acids, aldehydes and dyes, and may act as general protoplasmic poisons, by lowering the surface tension or by interfering with the bacterial metabolism. An *ideal antiseptic* should have selective action, high solvency for grease and pleasant odour. Even after the advent of sulphonamides and antibiotics, which also possess topical dosage-forms—nitrofurazone, gammaxane, D.D.T., benzyl benzoate, undecylenic acid, cignoline, chloramine T, halazone, dettol and several others, still find their uses as special antiseptics for aural infections, pediculosis, scabies, mycosis, psoriasis and as spermaticides. The local antiseptics are also used for hospital sterilisation, disinfection of rooms and appliances, fields of operation, wounds, burns, mucous membrane and sterilisation of water. The *disinfectants*, which normally possess nonselective actions, are usually used, in strong concentrations, for their bactericidal and sterilising effects on *inanimate objects*—drains, urinals, infected rooms and instruments, which can stand the effects of chemical antiseptics.]

A real counterpart of chemotherapeutic and antibiotic drugs, acting principally on localised infections, as against the systemic ones, in the case of the former. The following are the important groups:

- (a) General as well as special local antiseptics and disinfectants.
- (b) Scabicides, fungicides and ectoparasiticides of dermatological importance.
- (c) Insecticides.
- (d) Spermaticides.

The local *anti-infective drugs* combat localised infections, whereas the disinfectants are meant for the sterilisation of instruments, drains and urinals. The local and systemic antiseptics are thus complementary to each other.

Historical: This is lost in antiquity.

- (a) The Egyptian embalmers knew about the decomposition of dead bodies and preserved them with salts, spices and essential oils. Hippocrates used wine and vinegar for the dressing of wounds.
- (b) Ambroise Pare and Simmel-Weiss, confronted with the problem of puerperal sepsis and war wound, successfully used chlorine as antiseptic, long before the actual discovery of local antiseptics, in the 19th century.
- (c) Following the work of Pasteur and Koch, Joseph Lister established the use of carbolic acid as an antiseptic. The concepts of sepsis, asepsis and antisepsis were firmly established from this and others' work. In a review of Lister's work at the end of the last century, B.M.J. very correctly stated that Lister's discovery had outweighed the loss of lives from all the wars of that century.
- (d) In 1903, Rideal and Walker, introduced the technique of evaluation of antiseptics.

CLASSIFICATION

PHYSICAL AGENTS:	Dry and moist heat, U. V. rays, supersonics, osmotic agents.
SOAPS AND CATIONIC DETERGENTS:	Benzalkonium, benzethonium chloride, cepryn.
PROTOPLASMIC POISONS:	Metallic salts—Hg. Ag. Halogen derivatives, Iodine and chlorine. Also phenol, resorcinol and thymol.
OXIDISING AGENTS:	H ₂ O ₂ , KMNO ₄ , Pot. chlorate, sodium perborate.
ALCOHOLS, ACIDS AND ALDEHYDES:	Rectified spirit, boric, salicylic, mandelic and benzoic acids. Formaldehyde and hexamine.
ANTISEPTIC DYES:	Acridlavine, proflavine, methylene blue, gentian violet, crystal violet, pyridium.
MISCELLANEOUS AGENTS:	Sulphur, benzyl benzoate, ichthammol, Chrysarobin.

These antiseptics can also be grouped *therapeutically* from the nature of their uses:

- (a) Surgical antiseptics and disinfectant, (b) Skin antiseptics,, (c) Urinary antiseptics, (d) Pulmonary antiseptics, (e) Intestinal antiseptics, (f) Scabicides, antifungal and antipedicular agents.

Mode of Action: It differs according to the nature of the agents used:

- (a) The physical agents usually act by coagulation and denaturation of proteins.
- (b) Soaps and detergents lower surface tension and thus help in the penetration of drugs into the germs, which are then mechanically removed.
- (c) Heavy metals and many organic compounds act as protoplasmic poisons by chlorinating or iodising the same or as metal protein combinations.
- (d) The halogen compounds oxidise and precipitate bacterial proteins. Their actions are reduced by organic matters.
- (e) The synthetic dyes possess high penetration power for bacteria and interfere with their metabolism.

The *velocity* of antiseptic action depends on the following factors— (a) concentration, (b) temperature, (c) length of contact, (d) species of bacteria and (e) presence or absence of organic matters.

The expectations from an ideal antiseptic thus are great and they should possess, at least, some of the following characteristics:

- (a) Stable, powerful and penetrating action.
- (b) Specific, non-toxic effect, with high solvent power for grease.
- (c) Pleasant odour and colour.

Such selective actions for organisms, without disturbing the normal healing process, are not ordinarily very easily attainable and consequently, one has to be satisfied with the nearest approaches only.

Methods of Evaluation: (a) *R. W. coefficient* (b) *Chick-Martin tests*
In the former, the relative strength of any new antiseptic is measured in terms of carbolic acid, against the *Rawling strain* of *B. typhosus*, both the standard and the test antiseptic agent being made in 10-fold serial dilutions for inoculation, with the broth culture of the organism, by a standard-sized loop of specified diameter. The highest dilutions

at which the growth is inhibited in both, indicate their relative efficacy and potency, from which, the coefficient is worked out. This ratio should preferably be at least 10, for any good disinfectant action.

SOAPS AND DETERGENTS

These are surface-acting disinfectants meant for the sterilisation of skin, instruments and syringes. They may be considered under two groups:

- (a) *Anionic* detergents like ordinary soap, which is meant for the cleansing of skin and removal of bacteria.
- (b) *Cationic* detergents belonging to the alkyl-pyridinium groups.

Benzalkonium Chloride: (a) 0.1 % concentration is suitable for the sterilisation of skin and superficial injuries and (b) 0.05 % for the sterilisation of the mucous membrane.

Benzethonium Chloride: 0.1—0.2 %, is used for the skin, nose and the eye. *Cetyl pyridinium chloride:* 0.1—0.5 %, is used for the sterilisation of the field of operation.

All of them act mechanically, as well as, by lowering the surface tension of bacteria. They are to be used after complete removal of the soap from the surface of the skin.

ALCOHOLS

Ethyl Alcohol: In a strength of 70 %, it is a good antiseptic for skin and glass instruments. A mixture of ethyl and propyl alcohol, is a potent antiseptic and isopropyl alcohol is still better and does not disturb the potency of insulin. None of the alcohols, however, is effective against spores.

BORIC ACID

It is prepared from the native borates. An unctuous, white powder. *Dose:* 0.3—1 gm. Solubility in H_2O —1:25; In glycerine—1:4. *Preparations*—(a) Boroglycerine—33 % (b) Ung. acidi borici—10 %.

It is a non-irritating, mild antiseptic for skin, gastrointestinal and urinary tracts and is used for (a) surgical dressings, oral antiseptics and for mercurial salivation.

FORMALDEHYDE

Liquor formaldehyde containing formaline 40%, is a colourless and pungent liquid, soluble in water.

Actions and Uses: (a) An irritant, caustic and a protoplasmic poison, 10% solution is used for the fixation of tissues and 0.5% solution is sporocidal in 12 hours. It is effective against tubercle bacilli as well as, viruses. (b) It is also used for the conversion of toxins to toxoids, by combination with the amino group. (c) It does not lose its potency in the presence of organic matter and is also a useful room disinfectant, at a concentration of 20 gm/2000 cu. ft. area.

COALTAR DERIVATIVES

A large number of fractional distillates, at different boiling points, are available for use as common and special surface antiseptics. They comprise phenols, cresols and resorcinols.

Phenol (C_6H_5OH): It is obtained by fractional distillation of coal tar or by synthesis.

Actions: *Locally*—it imparts a sensation of numbness and tingling and may cause even gangrene on prolonged exposures. It is a comparatively weak antiseptic and does not kill *B. typhosus* even in a concentration of 1:200. Its bactericidal action is reduced by 10% in the presence of organic matter, as against 90%, with metallic antiseptics.

Internally—it is a central stimulant, producing convulsions, followed by depression and respiratory paralysis. It is excreted in a conjugated form, rendering urine smoky. This is due to its oxidation to catechol and hydroquinone.

Preparations: (a) *Phenol liquifactum*—1-3 drop. (b) *Unguentum*—3%, (c) *Suppository*—60 mg. (d) *Phenolated calamine lotion*—1%.

Uses: (a) Antiseptic hand wash—2.5% (b) Preparation of vaccine—0.5—1% (c) Also antipruritic and cauterising agent.

Cresol: There are three *isomers*—para, meta and ortho-cresols, collectively known as *tricresol*, which is three times more potent but less toxic than phenol. Presence of organic matter also diminishes its activity. A 2% solution is used for the disinfection of hands, utensils and excreta. *Lysol* and *eusol* are proprietary preparations.

Chlorocresol: is obtained by the chlorination of metacresol and is used as a preservative of injection solutions, in 0.1—0.25% concentration.

Chloroxylenol: or para chloroxylenol; white crystals with characteristic odour; Solubility: 1:3000; more in organic solvents. *Liq. chloroxylenolis* or *dettol* is a proprietary preparation, containing terpinol, alcohol and ricinoleic acid. It is a potent germicidal but organic matter disturbs its action. It is relatively non-irritant to skin and mucous membrane and does not coagulate proteins. Dettol cream—30% in tragacanth base, is used as an antiseptic for hand and vulva.

Hexachlorophen: A trichlorophenol derivative; it is soluble in alcohol, acetone and dilute alkalis. It is non-irritant and is used for pre-operative scrubbing and preparation of skin, in a concentration of 0.5 to 1% solution. It has a corrosive action on the epidermis and is used in psoriasis as 5%—10% ointment. It is also used in dandruff and seborrhæic dermatitis as 1-10% lotion.

R.W. values of Coal Tar Antiseptics: Phenol⁻¹, Orthocresol⁻²⁵, Chloroxylenol⁻³⁸, Trichlorophenol⁻⁶⁰, Tetrachlor orthocresol⁻²⁵⁰.

Pyrogallol: It is a trihydroxy benzene derivative and a powerful reducing agent. It possesses important fungicidal effect and is used in ring worm in the form of 5 to 10% ointment.

Picric acid: Trinitrophenol, a local anodyne, antiseptic and astringent, which stimulates the growth of the epithelial tissues. It leaves a yellow stain on the site of the application.

Thymol ($C_{10}H_{14}O$): It is an alkyl derivative of phenol and is used in—(a) Epidermophytosis as 1% sol. in alcohol, containing cinnamon oil and salicylic acid. (b) Ringworm—2% powder with boric acid and ZnO.

Tars: There are two important varieties—(a) Coal tar or *Pix carbonis* and (b) Wood tar or *Pix liquidum*.

Pix carbonis: A viscous liquid containing benzene, phenol and naphthalene. *Liq. picis carbonis*—5-10% ointment or lotion, is used in chronic eczema and *Pix liquidum*, containing cresol and guaiacol. *Dose:* 2-10 m. and *Syr. picis liq.* 0.15 to 0.6 ml., are used in chronic bronchitis and, bronchiectasis.

Actions: *Externally*, tar is a local antiseptic and a vascular stimulant in chronic psoriasis. *Internally*, during excretion, it acts as a disinfectant and deodorant, checking expectoration in chronic bronchiectasis. On prolonged use, it may upset digestion.

Creosote: is obtained by the distillation of beachwood. It is a colourless, oily liquid, with phenolic odour and acrid taste. It contains guaiacol and cresol. *Dose:* 0.15-0.6 ml. It is an antiseptic, parasiticide

and a local anodyne. It is sometimes used as a stimulant expectorant and also as a preservative of wood.

Ichthammol: A derivative of 'pitch', containing 10% sulphur, in the form of sulphonates. Brown, viscous fluid, with a strong odour and emollient action. A 10% ointment is sometimes used in (i) Chronic inflammations, (ii) Psoriasis, (iii) Erysepelas and (iv) Lupus erythematus.

HALOGEN ANTISEPTICS

Iodine, chlorine and its derivatives are the important members.

Inorganic Iodine: It presents itself as heavy, bluish-black prism with characteristic odour. It is slightly soluble in water as iodide and iodate salts.

Preparations: (a) Liq. iodis fortis and mitis—10% and 2.5% respectively, the latter known as, tincture iodine.

(b) Liq. iodis aqueous or Lugol's solution—5%. *Dose:* 0.3-1 ml.

(c) Pigmentum Iodi Co.—*Mandle's paint*, containing I, KI and glycerine, in pipperment oil.

Actions: *Externally*—(a) A rubifacient and vesicant for skin and mucous membrane, (b) A protein precipitant, (c) Free iodine acts as a fungicide.

Internally, it is converted to iodide in the G.I. tract and excreted in urine, sweat and sputum. The free iodine acts as an irritant. It produces vomiting and skin rashes, for which sodium thiosulphate and demulcents are used as antidotes and soothing agents.

Uses: (a) Tinct. iodine is an antiseptic and antiphlogistic for skin and joint troubles.

(b) Iodex is used for the resolution of fibrous tissues in chronic inflammatory conditions.

(c) Mandle's paint is used for tonsilitis.

(d) Lugol's iodine is used for thyrotoxicosis. It improves nervousness, perspiration, palpitation and insomnia, in 25% cases.

IODOFORM (CHI_3)

'Tri-iodomethane' is prepared by the interaction of iodine on acetone. It has lemon-yellow, shining crystals of disagreeable odour and taste. Solubility in 1 in 8 of ether. *Dose:* 30-100 mg.

Suppository, oculentum, BIPP and ZIPP: The uses of all these

preparations have almost been completely discarded, due to the conspicuous odour and inefficacy of these preparations.

CHLORINE COMPOUNDS

A number of substances, liberating chlorine, are used as antiseptic and disinfectants. They react on the ions of the amino groups of the germs, forming 'chloramines'.

Chlorine is germicidal in a concentration of 0.1-0.25 parts/million, in half an hour. Its R. W. value is 150-300. Presence of organic matter disturbs its action. The combination is called 'chlorine demand'. Acidity converts chlorine to hypochlorous acid, which is the active principle.

Calx Chlorinata: It is prepared by the interaction of chlorine on slaked lime and contains 30% of chlorine. Dull-white powder, characteristic smell, losing its property completely in one year. Bleaching powder is very irritant and is used for the disinfection of (i) Drains and urinals (ii) Sterilisation of drinking water (1 drachm/pint—1 t.s.f./2 gallons) (iii) Disinfection of swimming pools—0.2 parts/million.

Hypochlorite Solution: It is too strong for living tissues. Surgical solution of chlorinated soda i.e. modified Dakin's or Labarraque's solution, containing 2.5% NaOCl, are mostly used.

Uses: Freshly made solutions are sometimes used by *Carell's technique* of continuous irrigation for the removal of necrotic tissues of war wounds and also as *foot bath* in epidermophytosis.

Chloramines: These are organic compounds, liberating chlorine slowly in the body, their actions being less disturbed by organic matter. They are longer in action and less irritant for the tissues.

Chloramine 'T': containing 12% of active chlorine, does not decompose readily and is 4 times more germicidal than the hypochlorite solution. It is used for the (i) Irrigation of wounds—1-2% (ii) Gargle—0.1-0.2%.

Dichloramine 'T': contains 38% of active chlorine. In paraffine base, as 2-5% spray, it produces sustained antiseptic action.

Azo-chloramid: It contains 38% of active chlorine and is more active than chloramine. A solution of 1 in 2000 or 3000, is used in therapeutics.

Halazone: 1 in 2 to 5 lacs, sterilises polluted water. Tablets of 4-8 mg. 1-2 tabs/lit. of water can be used in camping for the sterilisation of water in 5 mins.

Succin chloramide: It contains 26% of chlorine and is available in 120-300 mg. tablets. It acts on *E. coli* and T.A.B. organisms.

OXIDISING ANTISEPTICS

They act by the release of nascent O_2 , which oxidises bacterial protoplasm. (a) Hydrogen peroxide (b) Potassium permanganate, (c) Potassium chlorate and (d) Na perborate, belong to this group.

Liq. Hydrogenii Peroxidi (H_2O_2): is prepared by the interaction of Ba peroxide, H_2SO_4 and water. It is a colourless, odourless liquid, decomposing in the presence of organic matter. The official preparation contains 3% H_2O_2 in water.

Action and Uses: (a) A powerful antiseptic used for the cleansing of dirty wounds. The action stops with the cessation of liberation of O_2 , (b) It is used as a gargle and mouth wash for pyorrhoea and also in otorrhoea.

Potassium Permanganate ($KMnO_4$): is prepared by the interaction of CO_2 on K. manganate, Dark purple, prismatic, crystals, sol. 1 in 20. **Dose:** 5-180 mg. Liq. potassi permanganatis—1%. Condyl's fluid—0.5%. **Dose:** 8.15 ml.

Incompatibility: (a) Reducing agents (b) Iodides (c) Organic matter.

Action: An antiseptic, deodorant and an oxidising agent, possessing germicidal actions of short duration.

Uses: (a) Gonorrhoeal urethritis—0.01%.

(b) Hand and mouth wash—0.5 and 1% respectively.

(c) Snake and mad dog bites—application of concentrated solution or pure crystals.

(d) Alkaloidal poisoning—by gastric lavage.

(e) Roger's procholera treatment with—(i) Ca permanganate (240 mg/pint) ad libidum (ii) $KMnO_4$ pills—120 mg/half hour, till the stool is greenish (iii) Hypertonic saline.

Potassium Chlorate: White, crystalline powder, sol.—1 in 16.5; may explode if mixed with organic matter and subjected to heat or concussion.

Uses: Stomatitis—2-4% aqueous solution, as mouth wash.

HEAVY METALS

Mercury, silver, zinc and copper belong to this group. Copper and its preparations have already been studied in the 'Chapter of Haemati-

nics'. The preparations and antiseptic actions of the remaining three are detailed below.

MERCURY

The antiseptic preparations belong both to the organic and inorganic series.

Inorganic preparations act by (a) non-selective protein precipitating action of short duration (b) They corrode metals and are toxic after absorption.

Organic compounds are less toxic, less irritant, more permeable and more efficient in bactericidal action.

Mercuric Chloride: It kills *B. typhosus* in 10^{-6} in 24 hrs; 1 in 20000 in 20 minutes; 1 in 1000—in $2\frac{1}{2}$ minutes. With 3% faeces, 90% of its action is lost. It is used for (a) Hand wash—1 in 2000, (b) Sterilisation of instrument—1 in 1000 and (c) Pediculosis—1 in 1000.

Yellow Oxide of Mercury: Eye ointment—0.1%; Ammoniated Hg. ointment—5% used for impetigo, skin fungi and pruritus; calomel ointment—20% is used in syphilitic chancre.

Merthiolate or Thimarsol: The aqueous solution, 1 in 1000, is used for the sterilisation of instruments and also of wounds and ulcers. It is very little irritating.

Metaphen or Nitromersol: It is insoluble in water but soluble in alcohol. Solutions of 1 in 1000 and 1 in 5000, are used for skin and mucous membrane.

Phenyl Mercuric Nitrate: It is slightly soluble in water but more in oils and glycerine. It is 78 times more powerful than corrosive sublimate against Gram +ve cocci and 64 times more active, as a fungicide.

ANTISEPTIC ACTIONS

Drugs	Instru	Eye	Nasal mucous membrane	Urethra	Skin
Merthiolate	1 : 1000	1 : 5000	1 : 2500	1 : 5000	1 : 1000
Metaphen					
Organism	Merthiolate	Metaphen	Phenyl Hg. nitrate	Corrosive substitute	Mercurochrom-me
Gonococci	1 : 48000	1 : 48000	1 : 80000	1 : 20000	1 : 240

SILVER

There are three different types of preparations: (a) Inorganic, (b) Colloidal and (c) Silver-protein combinations.

The *inorganic* preparations; ionise readily and are caustic and astringent in action. In *colloidal* preparations, there is very little silver in ionised form and they are consequently, much less caustic. The immediate germicidal action is from the ionic forms and the sustained action is due to the silver-protein combinations. AgNO_3 has a germicidal action in a strength of 1:1000, whereas, colloidal silver 0.01 % is used for the irrigation of bladder and urethra.

Silver Nitrate: It is astringent, caustic, poorly penetrative and easily precipitated by chlorides. It is available in the form of sticks, solutions and eye drops.

- (a) Sticks: used for cauterisation of ulcers and granulating tissues.
- (b) 0.01 % solution is used for irrigation of bladder.
- (c) 1-2 % eye drops used in ophthalmia neonatorum.

Silver Protein Combinations: These are colloidal preparations in combination with proteins. Of the three preparations, *Protargol* is the strongest and ionises more than others. *Collargol* is a milder preparation and *Neosilvol* is a colloidal silver halide.

The colloidal preparations are non-irritant and demulcent and are used in ophthalmic and other conditions, as detailed below:

	Eye	Ent.	Gonorrhoea	Cystitis	Gynaecology	Rectum
PROTARGOL	2—10 %	0.5—10 %	0.1—10 %	—	2—10 %	0.1—10 %
ARGYROL	25—50 %	10.0—20 %	0.1—20 %	10—50 %	20—25 %	0.1—20 %

Toxic effects: Ordinarily, silver preparations are very little absorbed from the skin and mucous membrane but on prolonged use, they may cause pigmentation of skin, sclera and viscerae. This is known as *argyrosis* or the bluish-black slate coloured man. It occurs from silver-protein combination in the body. No treatment is available for this condition.

ZINC

It is present in foodstuff. The industrial poisoning is known as *brass founder's ague* characterised by nausea, vomiting, colic pain, fever, catarrh and joint pains.

Action: Astringent, corrosive, mildly antiseptic and can form colloidal solutions like Ag.

Zinc sulphate is used in 0.1-1 % solution as eye wash, in conjunctivitis, in 2 gm. doses as emetic and as nasal spray in poliomyelitis.

Zinc oxide: (ZnO) forms the basis of toilet powders, ointments and pastes. For dermatological uses, 25 % is used.

Calamine: It is impure ZnCO_3 and iron oxide, simply coloured.

Lotions and liniments are used as favourite soothing applications for irritable skin and dermatitis.

Uses: For conjunctivitis— ZnSO_4 and boric acid lotions; for *chagrinous dermatitis*—calamine lotion containing calamine, ZnO, glycerine and lime water and for *Prickly heat*—camphor, sulphur, ZnO, boric acid, kaolin and starch powders, all in equal parts, are used.

SYNTHETIC DYES

Not only in staining properties, but also in antiseptic action, micro organism demonstrate selective affinity for certain dyes. The following four groups deserve special consideration for their local antiseptic actions.

AZO DYES	Scarlet red, pyridium, prontosil
ACRIDINE DYES	Acriflavine, proflavine
RESANILINE DYES	Gentian violet, crystal violet methyl violet, brilliant green.
<hr/>	
FLUORESCINE	Fluoresceinum sodium, mercurochrome.

Scarlet Red: A 4-8 % ointment promotes epithelial growth over ulcerated surfaces.

Acridine Dyes: The amino derivatives are used as tablets of 20 mg. or as ointments or solutions. They are germicidal for Gram+ve organisms and gonococci and are active in the presence of serum and organic matter also. The flavines also act as urinary antiseptics. *Proflavine* is non-irritant and non-interfering for granulation tissue formation.

<i>Compounds</i>	<i>Lethal concentration for Staphylococcus aureus</i>	<i>Concentration reducing phagocytosis</i>
Acriflavin	1 in 150,000	1 in 600
Proflavin	1 in 150,000	1 in 500
Mercuric chloride	1 in 20,000	1 in 10000

Uses: (a) Surface wounds—1 in 1000 (b) Gonorrhoea—1 in 1000-1 in 10000, (c) Suppurative infections—1 in 500, (d) Urinary antiseptic—0.2 gm/os/daily.

Resaniline Dyes: These are triphenyl methane derivatives, acting specifically on Gram+ve organisms, at a concentration of 10^{-6} . They form precipitates on necrotic tissues and are useful in burns.

Gentian violet is used in enteric coated capsule for oxyuriasis. *Crystal violet*: solution or 1 % jelly for wounds. *For burns* 1 % gentian violet, and brilliant green with 0.1 % of acriflavine, as *three dye lotion*, is used. Gentian violet is also used in (i) Fungal infections, (ii) Eczematous dermatitis, (iii) Furunculosis and (iv) Prurigo.

Methylene Blue: tetramethyl thionine chloride, is dark green crystalline, freely soluble in water. It is dispensed as capsule or tablet of 10 mg. each. It is a weak antiseptic and bacteriostatic. In large doses, it can produce methaemoglobinaemia and in small doses the opposite effect. It may give rise to nausea, vomiting and diarrhoea. It is used as (a) urinary antiseptic (b) in cyanide poisoning and (c) for sulphonamide methaemoglobinaemia.

FURANE DERIVATIVES

Nitrofurazone: A lemon-yellow, tasteless, insoluble powder which is effective against Gram+ve and -ve organisms, in the form of soluble dressings, with carbowax and propylene glycol. As 0.2 % sol., it is sometimes used in infections of the external auditory meatus.

SPECIAL USES

With this background of knowledge of general uses of local antiseptics, it may be advisable now, to deal with some of the specialised fields of local uses of antiseptics, referring particularly to skin and other tissues, with a view to focuss the attention better on some of the more

special uses of locally acting drugs as (a) Pediculocide (b) Scabicide (c) Antimycotic (d) Insecticide and (e) Spermatocidal agents, detailed hereafter, before reviewing their overall applications in medicine, at the end of the chapter.

PEDICULOCIDES

It is a shameful condition, representing dirty and unhygienic condition, of living demanding early redress. There are three types of lice infesting the human body: (a) *P. capitis*, (b) *P. corporis* and (c) *P. pubis*. Though morphologically different, their response to drugs is non-discriminating. The following drugs are used (a) Gammexane 1%, (b) D.D.T. 10%, (c) Benzyl benzoate 25%, (d) Bornate (e) Benzocaine 10-30% and (f) Ammoniated mercury lotion 5%.

A mixture of D.D.T. 6%, benzyl benzoate 68% and benzocaine 12%; Tween 80—14% has been recommended by the Expert Technical Committee of W.H.O. to be the best for delousing the body. The emulsion is diluted with 5 parts of the water before applying to the infested part.

SCABICIDES

Though a number of drugs are available, the ones mostly used are: (a) Sulphur and (b) Benzyl benzoate.

The infection is caused by the itch mite, *Acarus scabiei* or *Sarcoptes hominis*, which penetrates the epidermis, burrows along the skin, laying eggs, all the while. The infection primarily effects the webbs of fingers and is accompanied by a peculiar itching, vesicle formation and secondary suppuration.

Sulphur: It is available in 3 different forms:

Sulphur sublimatus or 'flower of sulphur'. Dose: 1-4 gm. A 10% ointment is used in scabies and itches.

Sulphur precipitatum or 'milk of sulphur' 1-4 gm; Confection—45%; 0.25-0.5 gm. is used as a laxative.

Colloidal sulphur: Fine suspensions with pantothenic acid, is used empirically, I.M., in rheumatism.

Acne lotion: (2%) containing sulphur, glycerine and aqua rosac, is used in acne and seborrhoea. Similarly, sulphur, ammoniated Hg. and Ung. simplex, with salicylic acid, is also used for itches.

Benzyl Benzoate: A synthetic compound with powerful spasmolytic action, which is of direct nature. Dose: 0.5-1 ml. It is however, seldom used in spasmodic disorders of plain muscles.

In the form of a 25% ointment, it is frequently used in scabies after thorough scrubbing of the affected area with soap and water. It is frequently used in the form of emulsion with soft soap and alcohol.

Gammexane and thiouran monosulphide—25% emulsion, is also used for the same purpose. Similarly, crotamiton—10% cream and dimethyl thianthrene and dixanthogin 10% cream or ointment, are also at times used.

ANTIMYCOTIC AGENTS

Various types of fungal infections that affect the human body are: (a) Dermatophytosis of palms and soles. (b) Ring worm of scalp and body and (c) *Taenia versicolor* infection of the back and the chest, causing maplike designs.

Though a large number of drugs (a) Iodine (b) Hg. (c) Sulphur (d) Salicylic acid (e) Whitefields' ointment, containing benzoic and salicylic acids, are in use, since long, the following are considered to be the best in modern therapeutics.

Undecylenic Acid: A yellow liquid of characteristic smell, which is obtained by the distillation of castor oil. Ointments—2.5-5% are mostly used. Zinc undecylenate is specially useful for the "athlete's foot."

Chrysarobin: A mixture of neutral principles, obtained from goa powder, containing chrysophanic acid, is a powerful skin and mucous membrane irritant and parasiticide. It stains the skin and turns urine purple. A 2% ointment is used in ring worm, psoriasis, eczema and other taenia infections.

Dithranol Cignoline: It is similar to chrysarobin but less toxic, cheap and less irritant for the skin and the kidney. Ung. dithranolis—0.1% is used for ring worm, psoriasis and alopecia areata.

Sodium Thiosulphate: A reducing agent, also known as *Hypo*, is parasiticial in ring worm and taenia infections, in 10% strength. In a dose of 0.25 gm., it acts as an antidote for cyanide poisoning.

INSECTICIDES OR ECTOPARASITICIDES

These groups of antiseptics are used for the destruction of insects and vectors of infections. They are invaluable for the prevention of diseases.

Dichlor-Diphenyl-Trichlorethane or DDT: A non-volatile and sparingly soluble powder and is a *contact* and not a *repellant* poison like pyrethrum, for flies, bed bugs, lice, cockroaches and mosquitoes. Combined with pyrethrum, its action becomes quicker.

Toxicity: (a) skin rashes, (b) tremor, (c) liver necrosis and (d) convulsions.

Preparations: (a) Kerosene oil emulsions of 5%, (b) Watery suspension of 10%, (c) Solutions in organic solvents: DDT-1 part, benzyl benzoate 10 parts, benzocaine 2 parts, ethyl alcohol—100 parts, are the frequently used preparations.

Gammexane ($C_6H_6Cl_6$), the gamma isomer of hexachlor-cyclohexane, is a stable, insoluble powder, more powerful and quicker in action than D.D.T. An 1.5% dust is used for the disinfection of refuges, in camps and other similar places, as a preventive measure against the spread of any infection.

Pyrethrum or Insect Flower: The active principle is 'pyrethrine'. A kerosene oil extract is used as *flit* against domestic flies, cockroaches, bugs and mosquitoes. It is toxic for the spinal cord and is a *repellant* poison which paralyses the respiration of the insects.

Covell's formula: Pyrethrum extract, oil of citronella, gum tragacanth and water, in 20, 5, 4, 80 parts respectively, with 0.5% D.D.T., is often used in India as domestic insecticide, by spraying.

Dimethyl Phthalate: A colourless, odourless and oily substance, which does not cause any smarting of the skin and is a good mosquito and flea repellant.

Retentone: isolated from the leguminosae, is a *fish poison* and *diazol*—an organophosphorus compound and a specific inhibitor of cholinesterase, are also used as pesticides, already discussed, in the Chapter of irreversible cholinesterase inhibitors.

SPERMATOCIDES

The need for *population control* by various contraceptive methods, has not only been realised but great strides already made, in recent years. While they will be detailed in Chapter-55, it may be stated here that they include operative procedures, use of oral contraceptives, condoms, loops and also local antiseptics in the form of solutions, tampons and douches of dettol and other antiseptics, pessarids of quinine, effervescent tablets of chiniosol and also *Koromex* jelly, containing glycerine of starch, with one or more of the local antiseptics,

lactic acid, hexyl resorcinol and oxyquinoline derivatives, in different concentrations. None of these, however, is fully dependable.

THERAPEUTIC APPLICATIONS

Though the concept of spread of infections through micro-organisms was not easily acceptable to the medical professions, initially, very soon a time came, when antiseptics started to be used and abused almost in a ritualistic manner, forgetting completely the role of the defence and self cleansing mechanisms of the body. With proper selection and judicious use, while they very effectively combat and prevent the spread of infections, if it is otherwise, they can also be instrumental in disturbing the normal healing processes in the host and cause resistance formation in the pathogenic organism, of far-reaching consequences. As far as possible, it is better to avoid the use of antibiotic locally, which are meant for internal use, for risk of causing unwelcome drug sensitisation effects, in the host.

INFORMATION AT A GLANCE

HOSPITAL STERILISATION:	U. V. light, Propylene glycol, D.D.T.
DISINFECTION OF ROOM:	Phenyl, sulphur dioxide and formaldehyde vapour.
APPLIANCES:	Dry heat, moist heat, dettol, carbolic acid.
SKIN AND MUCOUS MEMBRANE:	Rectified spirit, merthiolet, cetrimide, Zephyran, hand creams containing soap detergents.
WOUNDS:	Alcohol, neomycin, bacitracin, tyrothricin, terramycin.
BURNS:	Triple dye lotion, sulphonamides, terramycin.
EXCRETA:	Carbolic acid.
OPHTHALMOLOGICAL USE:	Mercurochrome, silver nitrate, sulphacetamide, terramycin.
DERMATOLOGICAL USE:	Boric acid, sulphaniламide, potassium permanganate.
SCABIES:	Benzyl benzoate, sulphur, borax, tetraethyl tetramonosulphate.
PEDICULOSIS:	D.D.T., Hg, ammoniatum, gamma benzene hexachloride.
ANTIMYCOTIC AGENTS:	Salicylic acid, sodium thiosulphate, chrysophanic acid, gentian violet, Hg. ammoniatum, mycostatin.
INSECTICIDES:	D.D.T. gammexane, pyrethrum, dimethylphalate.
SPERMATOCIDES:	Dettol, citric, lactic and tartaric acids, oxyquinoline, hexyl resorcinol.

CHAPTER

50

PHARMACOLOGY OF IMMUNITY AND IMMUNO-SUPPRESSIVE DRUGS

GENERAL CONSIDERATION OF NORMAL AND ABNORMAL IMMUNITY RESPONSES IN THE BODY. ACTIVE, PASSIVE, PRIMARY, SECONDARY AND DELAYED HYPERSENSITIVITY REACTIONS. ROLE OF VACCINE, SERUM, PHAGE AND GAMMA GLOBULIN. IMMUNOLOGICAL ANOMALIES, AUTO-IMMUNE DISEASES AND IMMUNO-SUPPRESSIVE AGENTS

[Immunity is a highly specific defence mechanism produced by antigen-antibody reaction. The antigen may be a dead or attenuated micro-organism, a toxin or a foreign protein. The immunological responses may be active, passive, primary, secondary or delayed and for varying periods. Some of the important vaccines are—Small pox, T.A.B., D.P.T., and B.C.G. and used for *prophylactic* purposes before an epidemic. *Gamma globulin* is used for poliomyelitis. The *sera*, obtained by immunising horses with gradually increasing doses of antigens, are used for *curative* purposes in diphtheria and tetanus. The *phages* containing living organisms—cholera, typhoid and enterophages, are not used in therapeutics, any more.

However important these responses may be, they may sometimes overshoot and create surgical problems of graft or organ transplant rejections. Under abnormal conditions, they may also induce *auto-immune disease*, like haemolytic anaemia, rheumatoid arthritis, lupus erythematosus etc. For combating these eventualities, *immuno-suppressive* agents, which are some of the anti-leukaemic, cytotoxic agents, a few antibiotic and corticosteroids, are sometimes used. Their efficacy in surgery is problematic and their role in auto-immune diseases, is insignificant, if not nil.]

General Considerations: In this chapter, not only the active protein group of immunity drugs of vaccine, serum, phage and gamma globulin, but also the recently developed immuno-suppressive agents, used in surgery and auto-immune diseases, will be dealt with.

With the discovery of chemotherapeutic and antibiotic drugs, though the therapeutic uses of some of these drugs have been somewhat restricted, their preventive value nevertheless remains almost unchanged, in view of the fact that chemotherapeutic and antibiotic drugs are not efficacious in all the infections and are also not capable of inducing any immunity reaction. Further, recent advances in our knowledge

of immunology and its intricate cellular mechanism of action, have started unveiling newer aspects of immunological disorders and approaches to drug therapy, as in the cases of tissue grafting, organ transplantation and autoimmune diseases.

The animal body is endowed with special mechanisms of defence against outside infections. The pathogenic organisms or their toxins, contain active proteins, capable of producing *antibodies*. Hence the name *antigens*. These are specific substances, resembling enzymes in action, denatured by heat and can detach their active groups to be anchored to other proteins. This type of reaction for the formation of antibodies, is known as *immunity reaction*. The reaction is highly specific and comparable to the functioning of individual keys for individual locks.

Immunity may be of *two kinds*: (i) *Natural* or race-species oriented, as in the cases of goats and dogs not getting tuberculosis easily, hens having natural immunity for tetanus and rabbits for atropine poisoning. This immunity, however, is not absolute and can be overcome by massive doses of germs or toxins. (ii) *Acquired*—This is induced artificially by the introduction of antigens or antibodies in the form of dead or attenuated organisms or their toxins, getting antibodies formed in the body by its own reactions and is known as *active immunity*. The immune bodies may also be produced in another animal with gradually increasing doses of antigens and the ready-made antibody supplied to a patient for cure or immunisation. This is known as *passive immunity*.

The *antigens* represent a wide variety of substances—dead or attenuated viruses, toxins, snake venom, ricin, abrin and several other substances of proteinous nature, capable of producing antibody reaction in the animal organism and with increased incidences of allergic disorders, newer substances endowed with antigenic properties, are being detected, every now and then. The toxins are generally of *two types*, *endotoxin* which is contained mostly in the body of the germ and liberated when crushed or lysed e.g. tubercle bacillus and pneumococcus and *exotoxin* as in diphtheria, tetanus and botulinus bacilli, being continuously poured into circulation producing pathological changes. These toxins, in general, are extremely potent, the L.D./Kg. of diphtheria toxin for guinea-pig being 0.001 mg. and of botulinus toxin for mouse— 10^{-6} mg.

Concept of Immunological Apparatus: In this general context, it is now possible to peep into some of the inner mechanisms of immunological responses at cellular and biochemical levels. The animal body is

endowed with ability of recognising the foreignness of any substance, with great precision. This cellular recognition is an immunological event of great significance and this new concept is not only being increasingly studied in recent years, but it has started unveiling fascinating information on the mysteries of mechanisms of immunological reactions, in animal organism.

On hypothetical ground, these immunological events can be explained in terms of an *immunological apparatus* which might have an (a) afferent (b) central and (c) efferent components, for its coordinated functioning.

Afferent component: It consists of phagocytes or monocytes, macrophages and fixed cells, in liver and spleen. Their chief function is to trap the antigen and transport it to lymphoid organs and reticulo-endothelial cells. The immune responses would then depend upon the type of antigen—good or otherwise. Ovalbumin and globulin are good antigens, whereas nucleoproteins and lysozymes are poor ones. The quantity and number of the antigenic stimulus, time-interval between them and finally, the duration and persistence of antigenic effects, would subscribe to the immune responses, achieved.

The next event is the processing of the antigen in *lysosomes*, which are cellular organelles, containing hydrolytic enzymes. Its most important and uncontroversial function is to digest the material, taken up by the phagocytes and pinocytes and thereby increase its antigenicity. Chloroquin and prednisolone have been found to inhibit the lymphocytic transformation by phytohaemagglutination, *in vitro*.

Central component: It chiefly consists of plasma and other cells, present in lymphoid organs, which respond to many, if not all the antigens, under the direction of the intriguing *thymus gland*, at least initially, showering and training them in the early stages, in respect of immunity responses, by the *thymic humoral factor* and thereafter, carry out its own assignment independently. The thymus thus has a great role to play in the functioning of the immunological apparatus, in the body, at least in its initial set up of organisation.

Both plasma and lymphoid cells are involved in antibody synthesis. Various theories have been postulated for this synthesis. Antigen may act as a *tear plate* for the antibody or may stimulate selectively the proliferation of preexisting antibody formation cells. *IgM* is the most primitive immunoglobulin and the first to be produced by the lymphoid organ cells. Adsorption of antigens to it results in the *primary response*—i.e. the response when the antigen meets the immunologically competent cells, for the first time. It is also known as *IGS* immunoglobulin. *IgS* is the immunoglobulin formed chiefly by the plasma cells and is involved in the *secondary response*, which is characterized by a higher

circulating titre of antibodies and this occurs at a shorter interval than in primary response, after its exposure to the antigens.

Efferent component: This includes the interaction of the antibody with the accessory factors like complement, intracellular and extracellular enzymes; permeability factor like histamine, serotonin, bradykinin, S.R.S. anaphylotoxin and other polypeptides, which are responsible for this response.

The immunologically competitive *small lymphocytes* under the influence of the antigen, may result in the formation of large basophilic cells, which in turn, may give rise to the immunologically activated, small or sensitized lymphocytes. These sensitized cells then infiltrate the target area and cause immunologically specific inflammatory reactions of characteristic histologic appearances taking generally 2-4 hours, to develop. No circulating antibody can be detected and hence it cannot be passively transferred by serum but by mononuclear cells from the lymphoid system of a sensitized animal. This is called *delayed hypersensitivity reaction*. Allograft rejection reaction for solid grafts, is fundamentally identical with this last phenomenon.

From the foregoing, it is evident that even at the present stage of our knowledge, which is still preliminary, immunity formation is a very complex biochemical phenomenon. This defence mechanism which is essentially salutary at an optimal level, under balanced circumstances, is not free from the risk of immunity disorders, if functioning in excess, for which, *immuno suppressive drugs*, discussed at the end of the chapter, are required, for preventing the transplantation rejection episodes in surgery. Further, under certain circumstances, there is formation of *autogenous antigens* in the body, leading to *autoimmune diseases*, detailed hereafter, for which, drug therapy is still inadequate.

In the above perspective, the following will be briefly dealt with in the chapter:

- (a) Vaccines, Sera and Phages.
- (b) Immuno-suppressive drugs and
- (c) Autoimmune disorders and their management.

VACCINES

As stated earlier, these are the foreign proteins of dead or attenuated bacteria, viruses or bacterial toxins, which acting as *antigens*, produce, *active immunity*, in the body, and are mostly used as prophylactic agents, against certain infections. The credit of this original discovery goes to Pasteur.

The Vaccine may be—(a) ordinary (b) sensitised or serovaccine (c) detoxicated and (d) formolised vaccines. They are used parenterally, before an epidemic, producing *three types* of reactions: (a) *Local inflammation* (b) *General pyrexia* and (c) *Focal reactions*. The system takes some weeks to produce immunity. Their strength is tested by—(a) *Bacterial count in Brown's opacity tubes*, (b) *Animal experimentation*, ascertaining antigenic value against specific organisms.

Vaccinum Vaccinae: or *calf-lymph*, is obtained by previously inoculating the animal with the cowpox virus. The lymph is collected aseptically by scraping the pustules, treated with glycerine and supplied in capillary tubes. It is an opaque liquid which should not contain more than 5,000 organisms per ml. Kept in cold storage, the potency remains for at least 3 months and at room temperature, only for 7 days. *Dose:* 1 drop by sacrifice of skin. The eruption passes through the stages of *macules*, *papules*, *vesicles* and *pustules*, often with fever reactions. Secondary infections are not infrequent. It gives successful protection for 5-6 years against small pox but not against chicken pox.

Primo-vaccination should be given before the completion of one year, preferably even before 6 months and then every 5-6 years and before an epidemic. Post vaccinal encephalitis is rare but a serious complication, which occurs more frequently in cases of late primo-vaccination. No positive reaction after vaccination, may result from immunity already present or from the poor quality of the lymph.

Freeze dry vaccine: Dry small pox vaccine is nothing but a grinded scrap of calf or cow pox virus, grown in chick embryo. It is dried with a stabilizer in frozen form and sealed under vacuum. An ampoule contains 10-20 doses of dried small pox vaccine. It is dissolved in 50% sterile glycerine just before use. Its keeping quality and efficacy are the maximum.

T.A.B. Vaccine: It contains *typhoid bacillus*—1000 millions/ml. and *paratyphoid A* and *B* 500 millions/each/ml.

The germs are grown on agar medium, washed out, tested for purity, killed by heat or carbolic acid, tested for sterility, diluted to required strength and ampouled. *Dose:* 0.5 ml. and after 7 days 1 ml. S. C. It often gives violent reactions. The duration of immunity is usually for 1 year.

Cholera Vaccine: It is prepared with *Inaba & Ogawa* strains of cholera vibrio, in the proportion of 3:1. It is a carbolised vaccine, containing 8000 million organism/ml. *Dose:* Initially 0.5 ml. and after 7-14 days,

1 ml. The duration of immunity is for 6-8 months and less than one year, in any case. Sometimes only one injection of 1 ml. is advocated.

Antiplague Vaccine: (a) *Bouillon culture* of virulent *B. pestis*, grown at about 30°C, for 4 weeks, killed at 55°C and preserved with 0.5% phenol, it contains 2000 million organisms per ml. *Dose:* 1 ml. initially and then 2 ml after an interval of 7-10 days. The immunity lasts for 6-8 months. It gives violent reactions.

(b) *Living attenuated vaccine:* a single dose of a living attenuated strain gives more immunity than several strains of heat killed antigen.

Vaccine Pertussis: It is a sterile suspension of *Haemophilis pertussis*, Phase I culture, *Dose:* 20,000 million/ml, at intervals of a month.

Polio Vaccine: (a) *Salk vaccine:* It is the killed virus vaccine and is given in *two doses* of 1 ml. each, I.M., at an interval of one month.

(b) *Sabin vaccine:* It is a live attenuated vaccine, given in *two doses* of 1 ml. each, orally, at an interval of 5 weeks.

Measles Vaccine: (a) It is an *inactivated* vaccine by formalin. It is given in *three dose* I.M., at monthly intervals, in doses of 0.5 ml. or 1 ml. It gives protection for two years.

(b) *Live attenuated* vaccine is given as a single subcutaneous injection and it induces active immunity for 3 years.

(c) *Combined inactivated*—live virus vaccine—1-2 doses of inactivated vaccine, followed in 1-3 months by a dose of live attenuated vaccine, is also sometimes used.

B. C. G. Vaccine: (Vaccine of Bacillus Calmette-Guerin). It is a virulent bovine strain of tubercle bacillus isolated in 1902 by the above workers. On repeated passages through glycerine-bile-potato medium, it loses its virulence, after successive cultures and 30 passages, at intervals of 25 days. Calmette observed in 1921 that the strain was innocuous for most of the animals and was since tried as B.C.G. vaccine, in human beings. This vaccine which had produced infections in earlier days and was therefore not in use for many years, was later on more rigidly controlled for sterility, purity and virulence and has again come into use, after world war II, on an extensive scale, under the auspices of the Scandinavian workers and the World Health Organisation. The vaccination is carried out as follows:

For adults: After a preliminary sensitivity test, in children, by *old tuberculin* and P.P.D., 5 tuberculin units/S.C. (1 T.u. of P.P.D.=

.00002 mg. and 1/100 mg. of old tuberculin), if no reaction is observed. B.C.G. is given in a dose of 0.25—1 milligram/ml., the volume injected, being 0.1 ml./I.D.

For newly born babies: Within the first four weeks of life, the preliminary tuberculin test is not necessary and B.C.G. is given straight.

The standard wheal should be of 8 mm. diameter. The process should be rechecked after 5-6 years.

Antirabic Vaccine: Though it is usually given after the bite of a mad dog during the incubation period, it actually acts as a *prophylactic* vaccine. This is because, the incubation period in rabies is long.

The virus of the mad dog is passed through rabbit brain by subdural injection. This now becomes the *fixed virus* of Pasteur and non-infectious to man. The rabbit brain emulsion is then injected intrathecally, in sheep and when paralysis sets in, the brain is taken out, treated with 1% carbolic acid, emulsions of 2-5% made and sterility tested. The dead virus retains its potency for 6 months.

The course of treatment varies according to the site and severity of the bite. The usual dose is 5 ml, I.M. into rectus abdominis muscle, daily, for about a week. In severe cases, treatment with antirabic hyper-immune serum is given, in doses of 10 ml. around the wounds and also S. C. Twenty-four hours after the serum therapy, vaccine therapy is started with 10 ml. I.M. daily, for 14 days.

Yellow Fever: 17 D virus and *Dakar vaccines:* 1 ml. S.C. Antibodies appear in 7-10 days after the inoculation.

Epidemic Typhus: *Cox vaccine:* 2 doses of 0.5 ml. and 1 ml. I.M. After 4 weeks interval, a booster dose of 0.1 ml. I.D.

PROPHYLACTIC TOXINS

Besides the vaccines prepared with dead or attenuated organisms or viruses, a number of toxins are also used for preventive and diagnostic purposes. Because they are very toxic, modifications, for decreasing this toxicity while retaining their antigenic value, have been devised.

Toxinum Diphthericum Detoxicatum: The following are used for immunisation, against diphtheria.

Toxin antitoxin mixture	Toxoid antitoxoid floccules.
Toxin antitoxin floccules	Alum precipitated toxoid.
Toxoid antitoxoid mixture	Anatoxin or formolised toxin.

Of these, *anatoxin*, alum precipitated toxoids and *P.P. toxoid* are the most used. *Dose*: 0.2 ml followed after a month, by 0.5 ml. S.C.

Toxoid and *antitoxin floccules* are used in 3 doses of 1 ml. each, at intervals of 4 weeks. Between the 1st, 2nd and 3rd weeks, the 2nd and 3rd injections are given.

Toxinum Tetanicum Detoxicatum: It is used *prophylactically* against tetanus infection. There are two: (a) Tetanus toxoid (b) Alum precipitated toxoid. *Dose*: 0.5-1 ml. S.C. at an interval of 4-6 weeks.

They can also be *combined* with T.A.B. and cholera vaccine and given in 3 doses of 1 ml. each, the 2nd dose being given after one month, the 3rd dose after 6 months. The duration of immunity is for several years.

Triple Vaccine (D.P.T.): This is used simultaneously against *diphtheria*, *pertussis* and *tetanus*. It is a mixture of diphtheria and tetanus toxoids and pertussis vaccine. It gives active immunity. It is given in 3 doses of 1 ml. S.C., at one month's interval, between 4-6 months of age. A booster dose of 1 ml. is given at the age of one year.

CURATIVE VACCINES

Vaccinum Staphylococci: 1 ml, containing 100-1000 million organisms. *Dose*: 10-1000 million, at intervals of 3-7 days. Sulpha drugs and antibiotics have eliminated its use.

Vaccinum Acne: 5-1000 million of *Corynebacterium acne*, given at an interval of 5-10 days.

DIAGNOSTIC TOXINS

These are meant for the diagnosis of susceptibility of an individual to infection, as *control tests*, before any epidemic.

Toxinum diphtherinum diagnosticum, is used for the *Shick test* in a dose of 0.2 ml. intradermally.

Toxinum diphtherinum calefactum: This is used as a *control test* for diphtheria, intradermally.

Tuberculinum Priestinum or *Old tuberculin*, a filtrate from 6-12 weeks culture. The germ is crushed and toxin liberated. *Dose*: 1-5 mg. S. C. for diagnosis of latent T. B. infection.

Gamma Globulin: This is the normal human antibody fraction of pooled plasma, duly concentrated to the extent of 25 times. It contains

most of the antibodies present in human plasma and is used as a prophylactic measure in (a) measles and (b) poliomyelitis. *Dose*: 0.1 ml. or more/lb. of body weight. Smaller doses are advocated in milder epidemics and also during the terminal phases of an epidemic.

This new measure has completely changed the epidemiological picture of *measles* and is yielding promising results, though still in experimental stage, in *poliomyelitis*. It is definitely superior to the 'serum of the convalescent', in respect of safety, uniformity of potency and stability. It does not work in diseases, such as chicken pox, german measles or mumps, for which, adequate antibodies are not available in the blood. Attempts are being made now to prepare gamma globulin from the serum of the convalescent also, for this purpose.

BACTERIOPHAGE

These are a group of minute particulates, believed to be viruses, which pass through chamberlain L3 filters (bacteria do not) and possess the property of eating or lysing certain germs, for which, the name 'bacteriophage' has been given to it. They grow in alkaline medium.

Properties: (a) filtrability (b) ability to multiply indefinitely in presence of young cultures (c) antigenic value (d) resistance to heat and alcohol but susceptibility to acids and antiseptics. They were introduced by D'Herelle for curative uses in cholera, typhoid, dysentery etc. as (a) *Cholera*phage (b) *Typhoid*phage (c) *Dysentery*phage and (d) *Enterophage*. *Dose*: 2-5 ml./OS, thrice a day: along with alkalis.

Efficacy: Opinion widely variable and they are seldom used these days.

SERA

These supply readymade immune bodies from horse serum and are used both for therapeutic and preventive purposes. They constitute two important types:

- (a) *Antitoxic*—diphtheria and tetanus antitoxic sera.
- (b) *Antibacterial*—antipneumococcal and antimeningococcal sera.

The *first group* neutralises the exotoxins which are thrown into the circulation by the organisms. The *second group* invades and agglutinates the germs themselves containing endotoxins. All sera, unlike vaccines, confer immunity of a more temporary nature, for tiding over an immediate crisis.

IMMUNISATIONS IN COMMON DISEASES

<i>Disease</i>	<i>Vaccine</i>	<i>Age of immunisation</i>	<i>Dose</i>	<i>Duration of immunity</i>	<i>Booster dose or repetition dose and its interval</i>
SMALL-POX	Cow-pox lymph, Freeze dry vaccine	3-6 months	A drop on the scratch or multiple pressure.	3-5 years	Every 3 years.
TYPHOID & PARATYPHOID	T. A. B. vaccine	3-5 years or later.	0.5 ml. and 1 ml. I.M. after a week or 1 ml. single dose.	1 year.	Every year.
CHOLERA	Cholera vaccine	1-2 yr. or late; endemic or epidemic after a week or 1 ml. zones I.M. single dose.	0.5 ml. and 1 ml. I.M. endemic or epidemic after a week or 1 ml. I.M. single dose.	6-9 months.	6-12 months.
PLAGUE	Antiplague vaccine	Any age; in endemic or epidemic zones only.	Any age; in endemic 1 ml. and 2 ml. I.M. or epidemic zones after 7-10 days.	6 months.	6-12 months.
WHOOPING COUGH (Pertussis)	Pertussis vaccine	3 months to 3 years.	The doses of 1 ml. at one month interval.	2-3 years.	1 ml. I.M., every year, upto 4 yrs. of age.
POLIOMYELITIS	(a) Salk vaccine (b) Sabin vaccine	6 months 6 months	(a) 1 ml. I.M. and 1 ml. after 1 month interval. (b) 1 ml. orally and 1 ml. after one month.	Many years.	

MEASLES	(a) Inactivated virus vaccine	3-9 months	3 doses of 0.5 ml. I.M. each, at monthly interval.		
TUBERCULOSIS	B. C. G.	(a) within 1 mth. (b) At 10-12 yrs.	0.1 ml. I.D. 0.1 ml. I.M., if tuberculin reaction is negative. Usually 5 ml. I.M. daily for 14 days. 10 ml. S. C. and around the wounds.	10 yrs. or more —do— 6 months —	To be given again, only if the person becomes tuberculin-ve
RABIES	(a) Antirabic vaccine (b) Hyper immune antirabic serum.	Whenever indicated. Prior to vaccine therapy in severe bites.			
TETANUS	(a) Toxoid	3-5 months or later	3 doses of 1 ml. each S. C., at 4 week interval.	3-5 years or more	After 1-10 years and when exposed to infection.
	(b) A. T. S. (i) For passive immunity. (ii) For curative use	Whenever required.	1500 U. S. P. units I.M. after S.T. 50000 to 100000 units.	3-6 months.	—
DIPHTHERIA	(a) Toxoid	3-4 months, upto 12 yrs.	3 doses of 1 ml. each I.M. at one month interval.	3-5 years.	After 1 year and when exposed to the infection.
	(b) A. D. S. (i) For passive immunisation. (ii) For curative purposes.	Whenever required. —do—	500 to 2900 units I.M. after S.T. 3000 to 100,000 units.	3-6 months.	—
DIPHTHERIA PERTUSSIS AND TETANUS	Triple or D. P. T. vaccine.	3-5 months.	3 doses of 1 ml. each I.M. at one month interval.	3-5 years.	1 year.

Preparations: (a) Horses are the animals of choice because they offer large quantities of serum (b) their veins are easy for manipulation, (c) they yield high titre serum, rich in immune bodies.

The animal is injected with gradually increasing doses of toxins or germs. After some weeks when the blood is very rich in antibodies, as observed by the agglutination tests, the animal is bled every week. The serum is separated out, the globulin fraction is obtained by half saturation with ammonium sulphate and precipitation, dried and made into solutions of required strength and marketed in ampoules.

Assay: The potency and toxicity of the serum are measured against International Standards, by some of the following measures:

Protection test: (a) This is carried out by flocculation method, in which, the serum in different concentrations, is mixed with the organism under specified conditions. The highest dilution producing flocculation, indicates the titre and unitage, in terms of the International Standard for simultaneous comparison. (b) The *protection test* carried out in guinea pigs, against the lethal dose of the germs.

Toxicity test: This is carried out in mice, in the same manner, as for the chemotherapeutic drugs.

Antitoxinum Diphthericum: 500-2000 units/ml. *Dose:* (a) *Prophylactic:* 500-2000 units S.C. (b) *Therapeutic:* 10,000 units/S.C.

Antitoxinum Tetanicum: *Dose:* (a) *Prophylactic*—1500 units S.C. (b) *Therapeutic:* 50000 units S.C.

Antitoxinum Gas Gangrene Compositus: (Cl. welchii and oedematiens and vibro septicum) proportion 2:2:1 *Dose:* *Prophylactic*—10000 units and *therapeutic*—30000 units.

Antibacterial Sera: There were several—meningo, pneumo, anthrax, staphylococcal sera but with the advent of the chemotherapeutic drugs, they now seldom find any therapeutic use.

Antivenin: It is prepared with cobra and russel viper venoms, containing both neurotoxin and haemorrhagin, which are injected in gradually increasing doses, into horses and their serum collected. It acts better in russel viper bites.

Prescribing Hints: (a) The I.V. route is only to be considered in cases of extreme emergency.

(b) With I.M. injection, half concentration occurs in 5 hrs. while with S.C. injection, this takes 40 hours.

- (c) After I.V. injection of 10000 units of serum, a blood concentration of 2 units/ml. as against 1.3 units/ml. after S.C. injection, is attainable.
- (d) For the use of the serum, the dose should not be worked out on the basis of body weight but on the basis of severity of the infection. Further, children can stand almost the same dose as for adults.
- (e) In cases of serum, only 20% is lost/day and consequently frequent doses are not required.

Serum Sickness: This is a hypersensitivity reaction to foreign protein. The reaction which takes place after the 2nd injection usually, is characterised by (a) colloidoclastic imbalance, with B.P. fall, bronchoconstriction, asphyxia, (b) skin rashes of urticarial type, fever and headache (c) also joints pain, oedema etc., as in histamine allergy. Its management comprises curative measures with-adrenaline, Ca, gluconate, Na benzoate, atropine, antihistaminics and purgatives.

Prophylactic treatment: by *Besredka's method* of desensitisation with gradually increasing doses of 0.1-0.2-0.5 ml. at 15 to 30 min. interval, till the full dose is given on the 5th or 6th injection S.C. Ca and *adrenaline* injections after the full dose of serum, are also to be given. Usually, concentrated and purified sera give less reactions than others.

Vaccines are available for various other diseases also. Vaccinations for *yellow fever* and *epidemic typhus*, small pox, cholera and plague, the 5 pestilential diseases, are required under the International certificate of vaccination regulation, for persons embarking from endemic or epidemic zones to other countries.

IMMUNO-SUPPRESSIVE DRUGS

This new branch of study has emanated from the observations of rejection of *allo* and *heterographs* of tissues and *organ transplants*, in surgical procedures. As indicated earlier, this is related to the *immuno-reaction* in the body and its disorders, for which, the *immuno-suppressive drugs*, are being tried with mixed results. The same is also the case with *autoimmune diseases*, the nature of which also, has recently, been discovered to be due to the action of *autogenous antigens*.

Drug Therapy: The remedies tentatively in use for immunosuppression purposes are virtually the same as categorised as antileukaemic, cytotoxic and antimalignancy agents, viz. alkylating, antimetabolite, antibiotic

and hormonal agents, besides total irradiation of the body, in sublethal doses, for lympho-suppression, with doubtful results. Their mechanism of action, in this condition as well, is probably the same as for the haemopoietic elements—enzymatic, antimetabolic, antimetabolite-mediated through the intermediary of DNA and m-RNA in the cell nucleus. Most of these, however, are still hypothetical, as much as, the salutary effects of these agents, also are. Nevertheless, the following facts deserve to be taken into consideration:

- (a) Some of the drugs, inhibiting the primary response, prior to the administration of antigen are—*corticosteroids*, *cyclophosphamide*, *actinomycin*, *busulfan* and radiation, while those which inhibit this response after administration are the antimetabolites—
 - (i) Folic acid antagonist—*methotrexate*, (ii) Pyrimidine analogue—*FuDR*, (iii) Purine analogue—*6 M.P.* None of these drugs can effectively inhibit the *secondary response*.
- (b) *Delayed hypersensitivity reaction* can be inhibited by *cyclophosphamide*, which acts by inhibiting the lymphocytic transformation, whereas *methotrexate* inhibits the production of sensitized lymphocytes.
- (c) *Heterologous antilymphocytic sera*, the most powerful immunosuppressive agents yet described, enjoy the advantage or preventing the *secondary* set of reaction i.e. rejection of the graft, for the second time.
- (d) *Other immunosuppressive agents* are: (i) *Mitomycin*: It produces depolymerization of D.N.A. but is too toxic. (ii) *Chloramphenicol* blocks the R.N.A. (iii) *Puromycin* prevents amino acid transfer from t-RNA to m-RNA.
- (e) The bone marrow grafts are used in: (i) bone marrow aplasia (ii) acute leukaemia and (iii) also for assessing graft versus host reactions and immunological complications.

Therapeutic Status: 1. For *skin allo-grafts*: heterologous antilymphocytic sera prevent both primary and secondary set of reactions.

2. For *kidney transplantation*: *Azathioprine* is the drug of choice. It is given in a dose of 3-5 mg/kg. daily, for 7 days, prior to surgery and after grafting is over, the dose is reduced to 2-3 mg/kg. daily, for indefinite periods. If necessary, 6-MP. should be considered as the second drug of choice.

3. *Acute rejection episode*: It is due to the interaction of small lymphocytes with graft antigens. The form, in which, antigens are presented to the lymphocytes and the precise anatomical site, at which,

interaction occurs, are not known. Activated lymphocytes may be destroying the target tissues.

4. The major *morphological changes*, occurring in renal homograft rejection are: (a) Rupture of peritubular capillaries and venules by cytotoxic antibodies, resulting in ischaemia, tubular necrosis, fever and oliguria. (b) Arteriolar and arterial lesions. Other causes are— (i) Uncontrollable fungal, viral or bacterial infections, due to the lowering of resistance (ii) Hepatotoxic action of azathioprine.

The rejection episode can be averted by giving *actinomycin C*: 4-8 ug/kg by I.V. drip, every day, if necessary and *prednisone* 700 mg in 3 days. It acts by preventing the DNA dependent RNA transcription. Such a rejection episode does not occur in non-vascularized areas e.g. anterior chamber of the eye, in corneal transplantation.

Autoimmune Diseases: As indicated, they relate to immunity disturbances, created by autogenous antigens. Some of the accepted forms and drugs, tentatively used for them, are:

Idiopathic thrombocytopenic purpura	— 6 MP, thioguanine: azathioprine.
Autoimmune haemolytic anaemia	Corticosteroids, purine analogues: Cyclophosphamide.
Glomerulonephritis } Rheumatoid arthritis }	— The same as above.
Systemic lupus erythematosus	— 6 MP: azathioprine: N ₂ mustard: chlorquin.
Polyarteritis nodosa	— Same as above.

Limitations: These drugs should be used with great caution because of the dangers of high toxicity and lowering of the resistance, to infection. Hence their safe indications for use are in refractory cases only. High toxicity is due to their effect on the regenerating tissues, as they act by inhibiting either their growth or divisions. Most toxic effects are produced on the gastrointestinal tract and bone marrow.

In the present state, the margin of success and failure with these drugs, is very narrow. A constant look out for better screening procedures and judicious clinical trials of newer compounds, can pave the way for better understanding of this problem and the discovery of more specific and less toxic drugs than at present, would be the future solution, for this present disappointing state of affairs.

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SECTION

XI

VITAMINS, HORMONES AND ANTIFERTILITY DRUGS

CHAPTER

51

PHARMACOLOGY OF VITAMINS

PRINCIPAL GROUPS: FAT AND WATER SOLUBLE VITAMINS. ROLE IN THE PHYSIO-PATHOLOGY OF DISEASES. THEIR ACTION AND USES

[The vitamins are the accessory food factors of organic nature. They are effective in minute quantities and their inadequacy in food produces definite deficiency and subdeficiency states. They belong to two distinct groups: (a) Fat soluble—A, D, E, F and K (b) Water soluble—B Complex and C.

Vitamins A and D: are present in shark, cod and halibut liver oils. The first finds its use in xerophthalmia, xerosis and infective conditions, while the second which is concerned with calcium metabolism, is used in rickets, osteomalacia, healing of fractures and tuberculosis. *Vitamin E* is the *antisterility tocopherol* acetate, which is used in sterility, habitual abortion and muscular dystrophies, while *Vitamin K*, which is concerned with the coagulation of blood, through prothrombin level, is used in haemorrhages.

Vitamin B Complex: this comprises several members, and is concerned with cellular metabolism. *Thiamine* is the antineuritic and antiberiberi factor while, *riboflavin* is coenzyme and hydrogen acceptor and is used in nutritional disorders and seborrhoeic dermatitis. *Nicotinic acid* is used in peripheral vascular disease, skin trouble, radiation sickness and in drug toxicity conditions. *Pyridoxine* finds its uses in vomiting of pregnancy, agranulocytosis and myasthenia gravis, *PABA* is used in rickettsial diseases and as an antigrey hair factor; *pantothenic acid* in hair and skin troubles, *choline* and *methionine* in liver disorders, and B_{12} in P.A. and other megaloblastic anaemias.

Vitamin C or *L-ascorbic acid*, plays an important role in the oxidation—reduction reactions in the body and also as an antianaemic and anti-infective agent. It is used in scurvy and other deficiency conditions and also as a detoxifying agent in infective conditions, for healing of wounds and sometimes also in microcytic anaemias.]

Vitamins are 'accessory food factors', and are effective even in minute quantities for the maintenance of normal health and vigour. Hence the name *vitamin*. They are not usually synthesised in the human

body, excepting a few, by the intestinal flora and are made available to the body through diets. Their deficiency causes definite syndromes, which quickly improve on administration of vitamins, concerned.

Historical: Study of avitaminosis and discovery of vitamins are traceable in three distinct periods:

- Prior to 1912 — Recognition of gross deficiency effects in man.
- From 1912-25 — Analysis of vitamin deficiencies by animal experimentation.
- From 1925 to date— Chemical identification, synthesis and study of their roles as coenzymes in carbohydrate, protein and fat metabolisms.

The outstanding works of John Hopkins, Funk, Szent-Georgyi, McCollum, Osborn, Mellanby, Dam and many others, in these fields, deserve special reckoning.

Physiological Considerations: The vitamins are concerned with the (a) Chemical control of bodily functions (b) Normal metabolism of cells (c) Regulation of intricate enzymatic processes.

The main causes of their deficiencies are (a) deficiencies in food (b) inadequate absorption and (c) increased needs in childhood, pregnancy and during lactation.

Though with increased knowledge of dietetics, complete deficiencies have become rarer now, subdeficiencies are not infrequent and vitamin therapy does wonders in those cases.

In cases of gastritis and gastro-enteritis from chronic alcoholism, vitamin B₁ is inadequately absorbed from the G.I. tract. Similarly, in cases of malabsorption of fat, absorption of fat soluble vitamins, is grossly hampered. In the very same manner, absorption of vitamin 'K' is hindered by the absence of bile in the intestine.

CLASSIFICATION

FAT SOLUBLE—RELATIVELY THERMOSTABLE: Vitamins A, D, E, F and K

WATER SOLUBLE—RELATIVELY THERMOLABILE: Vitamins B and C.

VITAMIN 'A'

McCollum and Davis, in 1913, reported for the first time, on the role of the fat soluble vitamin A as growth factor in rats. It was observed

that dietary sources included preformed *Provitamin A* or B-carotenes, a yellow pigment, present in carrot and green vegetable. It is an unsaturated alcohol, easily oxidised to colourless vitamin A in the liver. Valuable sources of vitamin A are—liver, egg, dairy products and fresh water fish. Being fat-soluble, ordinarily, cooking does not considerably spoil its activity but prolonged and repeated cooking and rancidity, partially destroy its properties.

<i>Daily Doses</i>	<i>Units</i>	<i>Vitamin A</i>	<i>Units/gm.</i>
Adult	2,000	Butter	60
Child	4,000	Yolk of egg	30
Pregnant & lactating woman	6,000	Carrot, cabbage beans & milk	5-10
		Vegetable oils	Nil

PREPARATIONS

Sol. vit. A conc	4—40 mg	2,500—25,000 units
Oleum morrhuae	4—12 ml	1,100—600 units
Oleum hypoglossi	4—32 mg	1,500—12,000 units
Shark liver oil	0.2— 1 ml	1,500—7500 units

Assay: Vitamin A preparations may be tested—(a) *Colorimetrically* with antimony and arsenic trichloride (blue coloration) in a Lovibond tintometer or (b) *Biologically*, in rats, estimating the growth effect or (c) *Spectrophotometrically*—The International Standard beta-carotene, representing 1 unit/0.6 μ g. Synthetic vitamin A represents 3 million units/gm.

Metabolism: It is absorbed from the gut in the presence of bile and fatty acids, in 3-5 hours, according to bodily needs, after undergoing enzymic hydrolysis and conversion to alcohol. Liquid paraffin seriously interferes with its absorption, as vitamin A is dissolved in it and expelled. Absorption is 25% less for 'carotene'. It is stored in Kupffer's cells, the rat liver having 1 lac times more vitamin A than in other tissues of the body. In diseases, the storage is affected by less absorption, more utilisation and imperfect conversion of carotene to vitamin A. It is excreted mostly through urine. In health, excretion is insignificant. In pneumonia upto 3200 units/day, ceasing abruptly with the crisis.

Functions: (a) Vitamin A is essential for the maintenance of integrity and development of *epithelial cells*. It possibly acts as a prosthetic group of an essential protein structure of the epithelial linings.

Plate XLII

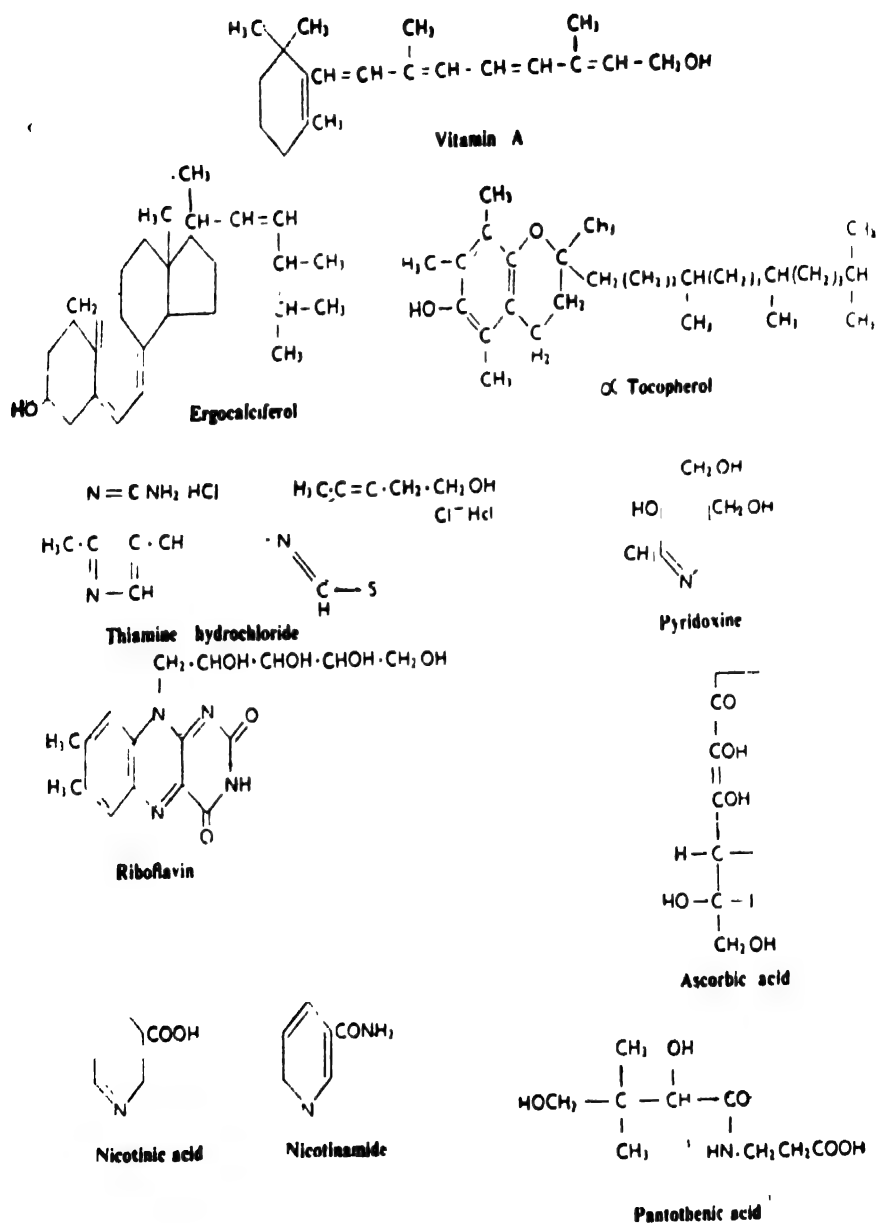


FIG. 111. Chemical structure of vitamins

- (b) It is required for the synthesis of the retinal pigment *rhodopsin* (visual purple), in which, a derivative of vitamin A combines with a protein. This combination is unstable in light but resynthesis takes place in the dark. Visual purple is essential for normal vision in dimlight.

Avitaminosis A: The earliest symptoms are—night blindness or *nyctalopia* and *hyperkeratosis*. The epithelial cells are atrophied and there is proliferation of basal cells and formation of stratified, keratinised epithelium. The important conditions are:

- (a) *Xerophthalmia*: It is secondary to pathological changes in the glandular epithelium with failure of mucous and lachrymal secretions, which lubricate the eyes. There is keratinisation of conjunctiva and cornea, followed by ulceration, leading to permanent opacity of cornea, with partial or complete blindness. The severe form is known as *keratomalacia*, which ultimately leads to *panophthalmitis*.
- (b) *Xerosis*: or roughness, dryness and toad skin, is due to keratinisation of epithelial tissues, with a tendency for formation of papular eruptions.
- (c) There is also atrophy of cells of *salivary gland* and *mucous membrane* of intestine. The growth of bones may be retarded.
- (d) There may be involvement of nervous structures with *demyelination* and symptoms of paresis, resembling lathyrism.
- (e) Retarded growth and atrophy of testes, ovaries, ulceration of gut, diarrhoea, pyorrhoea, urinary calculi and respiratory infections. It is therefore known as *anti-infective vitamin*.

Hypervitaminosis A: This may occur especially in *children*, due to very high intake. Swelling of bones, joints pain, hyperostosis of long bones, anorexia, pruritus, dry scaly lips and skin, sparse hairs, pigmentation and hypoblastic anaemia, may occur.

VITAMIN D

A fat-soluble sterol derivative, chemically related to cholesterol, sex hormones and cardiac glycosides. Vitamin D obtained from animal tissues is physiologically active. *Calciferol*, obtained by the ultra-violet irradiation of ergosterol, is vitamin D₂. The provitamin for D₁ and D₂ is ergosterol, which is found only in plants. *Vitamin D₃* has also been isolated, for which, 7-dehydrocholesterol, is the provitamin.

All these provitamins are converted to their corresponding vitamins by sunlight and artificial ultra violet irradiation.

Daily requirements/units		Source	Units/ gm.
Adults	300	Egg yolk	2-5
Pregnancy & lactation	800	Butter	1-4
Infants	700	Cream	0.5
Premature infants	1400	Milk	0.1
		Cod liver oil	85

PREPARATIONS

Calciferol tablet	(a) Prophylactic	0.1 mg. = 4000 units
	(b) Curative	1.25 mg. = 50000 units
Liquor calciferolis	(a) Prophylactic	1.3 ml. = 4000 units
	(b) Curative	.16 ml. = 50000 units
Oleum morrhuae	4-12 ml.
Extract maltcum oleomorrhuae	4-30 ml.

Assay: This is both *biological*, as well as, *Spectrophotometric* and detailed in Chapter 6.

Metabolism: Vitamin D is absorbed through all the surfaces of the body viz. skin and mucous membrane and also from all the routes of administration—OS, I.M., S.C. Bile acids help in its absorption. Nevertheless, about 25% escapes intestinal absorption. It is stored in the body and not metabolised and slowly excreted through milk and urine.

Functions: Vitamin D helps in the absorption of calcium and phosphorus and takes part in the calcification of bones. It activates the alkaline phosphatase, concerned with absorption, deposition and excretion of calcium and phosphates.

Avitaminosis: *Rickets*, in children and *osteomalacia* in adults, are important deficiency conditions. These are due to an inadequate absorption of calcium and phosphate from the intestine, which results in the failure of the matrix to ossify, leading to *disturbed bone formation* with swollen epiphysis, disappearance of the line of calcification, disorganisation of calcifying tissues and soft bone formation.

Defective dentition: The enamel and dentine are affected. The *Cu/Phos* ratio is altered. The presence of less blood calcium and greater phosphates, retards the formation of bones.

Mechanism of Action: In the absence of vitamin D, the gut content becomes more alkaline, Ca absorption is disturbed and whatever is absorbed, is excreted. The absence of sunlight disturbs the formation of ergosterol from the skin. *Parathormone* regulates *Cu/Phos* metabolism and by producing phosphaturia, depletes the body of the calcium, by metabolising it from the bones. Vitamin D helps in the absorption and utilisation of Ca from the guts. Presence of phytic acid in cereals, also disturbs Ca absorption with consequent decalcification. This has been detailed further in the chapter of calcium metabolism.

Hypervitaminosis: It is quite rare, as unlimited absorption of vitamin D through gut is not possible. It may occur only from the use of highly rich calciferol or irradiated ergosterol. In this condition, there is (a) loss of appetite, vomiting, diarrhoea and loss of weight (b) calcification of ovaries and formation of calculi. All these result from hypercalcaemia.

Cod Liver Oil: or *Oleo morrhuae*, is a pale-yellow liquid, with fishy odour. It contains vitamins A and D, essential fatty acids, cholesterol, traces of iodine, bromine and phosphorus. It is a bland oil which is easily absorbed and utilised in the body, when given in the form of an emulsion. It is used in rickets, chronic wasting diseases like tuberculosis and chronic bronchitis. *Halibut liver oil* is much richer in vitamin D and *shark liver oil* in vitamin A than cod liver oil.

Uses: Many and not always equally effective. Though the most important use is primarily in *rickets*, it is also used in many other conditions like (a) Parathyroid tetany, (b) Osteomalacia, (c) Healing of fractures, (d) Dental caries, (e) Lupus vulgaris and lastly (f) Upper respiratory tract infections.

Dental caries: Vitamin D and C are good protectives and also improve general health, nutrition and conditions of the teeth.

Osteomalacia: both calcium and vitamin D therapies are recommended.

Healing of fractures: Vitamin D-600 I.U. daily, particularly in old persons, with osteoporosis, is recommended.

Lupus: Streptomycin: 1 gm. with calciferol 100000 units daily for 6-9 weeks, sometimes gives good results.

Parathyroprivic tetany: Vitamin D stabilises the calcium disorder and corrects phosphorus metabolism. *Dihydro-tachysterol*, obtained by irradiation of cholesterol acts like parathyroid hormone and effectively mobilises calcium from bones.

Calcium and phosphorus absorption and metabolism are inter-related. When diet contains more phosphorus in the form of phytic acid, as in cereals, most of the Ca and Phos are not absorbed. The absorption is facilitated by Vitamin D and the acidity in the upper part of the intestine. Vitamin D also inhibits the excretion and increases tubular reabsorption of phosphates.

Rickets: Prophylactic: pure milk and milk products. Cod liver oil or halibut liver oil: 4-8 ml. Calciferol: 4-12 mg. Ostelin: 24-60 mg. Adexolin: 40 mg. daily.

Curative: (a) Ca rich diet but restricted carbohydrates and cereals. (b) Vitamin D: 2000-3000 I.U. daily, for infants. Radiostoleum or Ostelin: 60-80 mg./OS or I.M. (c) Iron and vitamin C for correcting the associated anaemia. Vitamin D increases Ca and phosphate absorption from the intestine, increases inorganic phosphates in the blood and causes tricalcium phosphate to be laid down in the skeleton. After a week's treatment, increased retention of Ca and phosphate occurs but x-ray picture shows calcification of bones after 3-4 weeks only.

VITAMIN E

Antisterility, fat soluble vitamin, it is present in wheat germ oil, embryos of seeds, green vegetables and eggs. The isolated crystalline principles are known as *alpha*, *beta* and *gamma tocopherols*, which are alcohols. *Alpha tocopherol acetate* is the most active amongst them.

Preparations: (a) *Ephynal*: Tablets of 3 mg. **Dose:** 3-10 mg. (b) *Phytopherol*, a racemic tocopherol, used in capsules of 3 mg.

Vitamin E		100 gm	
	mg.		
Brown bread	2	Wheatgerm oil	150-400
Wheat germ	27	Green peas	5
Butter	2	Sesame oil	5
Anchis oil	30		

Actions: Its deficiency, though rare, produces widespread structural and functional abnormalities of the reproductive and nervous systems,

as well as skeletal and cardiac muscles. The biochemical defects involve fatty acid metabolism and enzymatic disorders. Vitamin E is essential for nuclear activity and formation of chromatin. It is concerned with cell proliferation in general, embryos in particular, and also of the germinal epithelium of testes. Its deficiency has been found to produce death of the foetus and habitual abortion. However, it does not seem to increase normal fertility. In males, it may be associated with azoospermia and impotence.

It has also been found to produce degenerative changes in the anterior pituitary, with disturbances of gonads and prolactin. Further, its deficiency may lead to muscular dystrophies and degenerative changes in the cord. Vitamin E may prevent this process but is not a dependable curative. It does not improve myocardial degenerative changes.

Uses: Hardly of much significance: (a) Sterility. (b) Habitual and threatened abortion and also premature labour and placental haemorrhages; but not a sure remedy. (c) Muscular dystrophies with fibrositis: in 200-300 mg. doses; but also with undependable result.

VITAMIN K

Also known as the *Koagulation vitamin*, is another fat-soluble vitamin, discovered by Dam. It is available in K_1 and K_2 forms, as derivatives of *maphthoquinene*. It is a yellow oil, present in the photosynthetic parts of plants, alpha-alfa grass, cabbage, spinach, soyabeans and strawberries. It is also formed in the gut by bacteria and has now been synthesised. Its absorption is facilitated by bile salts.

Preparations: (a) *Menaphthone*: 10-60 mg. and *Acetomenaphthone* 10-60 mg. are *fat soluble* and used orally. (b) *Menadione sodium sulphate*: 0.5-2 mg., is *water soluble* and used S.C., I.M. and I.V.

Action: Vitamin K plays an important part in the formation of prothrombin.

Prothrombin + thromboplastin + Ca \rightarrow Thrombin.

Thrombin + fibrinogen \rightarrow fibrin, resulting in clot formation.

In the absence of vitamin K, the clotting time is enhanced, haemorrhages occur and prothrombin time is increased. In haemorrhagic diathesis, there may be vitamin K deficiency with hypoprothrombinaemia.

Di-coumerol and larger doses of salicylates, inhibit the synthesis of prothrombin in the liver, probably by competing with vitamin K on the receptors. The prothrombin time is increased. This process can be reversed by the administration of vitamin K.

- Uses:** (a) Obstructive jaundice with petechae and low prothrombin level.
 (b) Postoperative and neonatal haemorrhage.
 (c) It is useless in haemophilia.

VITAMIN B COMPLEX

A group of water-soluble vitamins, which are present in the yeast, marmite and cereals. Chemically, they are more than one entity but as they are soluble in water, they are grouped together. They are stable in acid solutions and are very complex in nature. The following are the important members:

Thiamine	Pentothenic acid	Inositol
Riboflavin	PABA	Folic acid
Nicotinic acid	Biotin	Cyanocobalamine
Pyridoxin	Choline	

THIAMINE

Aneurine or vitamin B₁, is a colourless, crystalline substance, relatively thermolabile, having a complex organic molecule, containing a pyrimidine nucleus and a thiazol ring. It is sensitive to ultra-violet light and is destroyed by oxygen, in alkaline medium.

Sources: It is found in animal and vegetable food stuff and is more concentrated in brain and germs of cereals. Sufficient quantity of thiamine is available to the body from beans, potatoes, green vegetables, carrots and eggs.

Action: In the form of *thiamine pyrophosphate*, it acts as a *coenzyme* to the co-carboxylase, which is essential for the oxidation of *B-keto-acids*. Lack of vitamin B₁, leads to the accumulation of pyruvic and lactic acids and pyruvic aldehydes, in the body. Thus carbohydrate metabolism is grossly disturbed and toxic symptoms produced, particularly in *nervous* and *cardiac* tissues, as they have a large carbohydrate turnover. Its *deficiency* leads to—(a) deranged carbohydrate meta-

bolism, (b) polyneuritis in pigeons, (c) retarded growth in the young rats, (d) dragging of limbs with paralysis of flexor-extensor muscles and (e) atrophy of lymphoid tissues.

Metabolism: Though it is *absorbed* through the G. I. tract, the absorption is much better after I.M. injection, because of the gastro-intestinal changes, accompanying the a vitaminosis. It is *stored* in muscle, liver, brain, kidney and heart. The major portion is utilised or destroyed in the body and only 10% is excreted through urine. About 1 mg. of thiamine is metabolised per day by the tissues and this is the daily requirements.

Toxic effects: Rather rare, unless very large doses are used, in which case, vomiting, nervousness, tachycardia and flushings may occur.

Avitaminosis B₁ : Produces *beriberi* in rice eating populations, using milled rice particularly, as the pericarp contains thiamin. The chief symptom observed, in this condition, is *polyneuritis*.

Beriberi is seen in two forms: (a) *Dry form* with wasting and nervous lesions. (b) *Wet form* with oedema and myocardial degeneration.

Infantile beriberi is due to vitamin B₂ deficiency in the mother and the mortality rate is over 50%.

Hypovitaminosis: This, in fact, is much more frequent and causes bradycardia, wasting of bowels, G. I. atony, distension, constipation and symptoms of autointoxication.

Preparations: (a) *Dried yeast tablets:* 6 gm., each gm. containing 0.12 mg of thiamine. (b) *Thiamine HCl* (i) Tablets of 1-2 mg. (ii) Inj. 25 mg/ml. Berin, betaxan and benerva are proprietary preparations.

Assay: (a) Rat bradycardia method, (b) Thiochrome fluorescence test. One unit of activity is contained in 3 μ g of thiamine standard powder.

Uses: Major indication is only *one*—*Beriberi*, the incidence of which is much on the wane. It is also used in (a) *Acute alcoholism* and *alcoholic neuritis* or *neuritis of pregnancy* and *S.A. combined degeneration*.

(b) *Cardiovascular disorders* of nutritional origin, with oedema
Dose: 10-30 mg. t.d.s.

(c) *Multiple hypovitaminosis States* viz. G. I. disorders, colitis, hypotonia and chronic diarrhoea.

In all these conditions it is desirable to administer a suitable preparation of vitamin B₁, *parenterally*, as the intestinal absorption is often unsatisfactory. After the deficiency state is removed, it can then be *orally* given.

RIBOFLAVIN

Also known as *lactoflavin* or vitamin B₂, it is a yellow crystalline powder, sparingly soluble in water and is present in milk, yeast and liver extract. Riboflavin performs the functions of *coenzymes*, in the form of *flavin mononucleotide* (FMN) and *Flavin adenine dinucleotide* (FAD). These enzymes catalyse the reaction of removing hydrogen from their substrates and therefore belong to the dehydrogenase group. In these enzymatic reactions, riboflavin phosphate, acts as 'hydrogen receptor'.

Its deficiency is known as *ariboflavinosis*. It causes inflamed and cracked lips or *cheilosis*, inflamed and sore tongue or glossitis, inflammation of the angles of mouth or angular stomatitis and inflamed pharynx or pharyngitis. In addition to these, there is seborrhoeic dermatitis with keratitis and also neurological disorders.

Human requirements in children is 0.9—2.5 mg/day; in adults 1.5—1.8 mg/day and during pregnancy and lactation: 2.5—3 mg/day.

Metabolism: It is absorbed from the G. I. tract and produces a high concentration in the kidney, liver and heart. About 20% is excreted in urine. It is synthesised in the intestine and is also present in bacterial cells.

Preparations : (a) Tablets of 1-10 mg. *Dose:* 5-10 mg/day. (b) Injection of 0.2 mg/ml.

Uses: Very limited. As *aribiflavinosis* is associated with other nutritional deficiencies like pellagra, consequently, vitamin B complex is more often used than the individual components.

NICOTINIC ACID

Nicotinic acid and its amide, *nicotinamide*, is white crystalline powders, slightly bitter and soluble in water. Nicotinic acid is synthesised by the intestinal flora and inhibited by sulpha drugs. It is widely distributed in plants and animal tissues—cereals, milk and yeast. Nicotinamide is incorporated in molecules of two important coenzymes—

Coenzyme I (DPN) and Coenzyme II (TPN). In both of these cases, the nicotinamide moiety acts as 'hydrogen acceptor'.

Action: (a) Its deficiency causes *Pellegra*, in maize-eaters, with glossitis or black tongue, skin troubles, mental disorders, insomnia, headache, palpitation, flushings, B. P. fall and macrocytic anaemia. (b) It produces vasodilatation and is therefore used in mild cases of hypertension. (c) It also lowers the blood cholesterol level.

Preparations: (a) *Nicotinic acid* 25, 50, 100 mg. tablets. (b) *Nicotinamide*: 25, 50, 100 mg. tablets or injections.

Uses: (a) *Pellagra*: 50 mg/b.d. after food or 20 mg.inj./b.d. (b) *Peripheral vascular diseases*. (c) For increasing C. H. tolerance in diabetes and reducing insulin dosages. (d) *Pruritis* and *dermatitis* of diabetics. (e) *Trigeminal neuralgia*. (f) *Irradiation sickness*. (g) *Toxic effect* of sulphonamides. (g) Treatment of *atherosclerosis*.

PYRIDOXINE

Also known as *vitamin B₆* or *Adermin*; it is present in germinated seeds, yeast, liver, fish and cereals. The daily requirement is hardly 3 mg. *Chemically*, it is a derivative of pyridine. In natural sources, it is present in 3 forms: (a) *Pyridoxin* (b) *Pyridoxal* and (c) *Pyridoxamine*. Any of these forms can be used by mammals. Its antimetabolite, desoxypyridoxin has been synthesised.

Action: It has hardly any pharmacological action of importance. In the body, it is active as phosphorylated pyridoxal or pyridoxamine. It serves as a prosthetic group in the enzyme system and is concerned with the metabolism of amino acids as transaminase, decarboxylase and transmethylase. It is also concerned with the metabolism of tryptophane, with a hydrolytic cleavage at the level of the indol nucleus. It is absorbed from the G. I. tract and about 50% is excreted in urine, in 12 hours, partly as an oxidised product, 4-pyridoxic acid and partly in the other 2 forms.

Preparation: *Pyridoxine HCl*: white crystalline powder, moderately soluble and stable. *Tablets* of 25 and 50 mg. *Inj.* of 25 and 50 mg/ml. They are assayed by the (a) *Growth rate* method in chick and also, (b) *Microbiologically*.

Deficiency syndromes: refer to the (a) *Skin* (b) *Nervous system* and (c) *Erythropoiesis*,

Dermatosis: (a) Seborrhoeic conditions of eyes, nose and mouth, accompanied by glossitis and stomatitis.

(b) Degenerative changes in the nervous system, lowering of E.S.T. and convulsive seizures, improved by pyridoxin and glutamic acid.

(c) *Microcytic, hypochromic* type of anaemia.

Uses: (a) Deficiency syndromes. (b) Radiation sickness (c) Vomiting of pregnancy (d) Various types of dermatosis, including arsenic dermatitis, (e) Sydenham's chorea (f) Agrabulocytosis. (g) Muscular dystrophy and sometimes (h) Myasthenia gravis.

In *hypermesis gravidarum* and irradiation sickness, it is used in doses of 100-200 mg. I.V., followed by 50-100 mg. orally, till the condition improves.

Pantothenic acid: A yellow, viscous oil, present in yeast, liver and kidneys. It is also synthesised by certain moulds. It is essential for nutrition and it acts as *coenzyme A* for transacetylation and detoxication of sulphonamides. *Calcium pantothenate* is a white, crystalline powder and soluble in water. Its deficiencies cause—(a) retarded growth, (b) coarse fur and (c) red nose. The *daily requirement* is 5-10 mg. Ca pantothenate. It is used for premature greying of hair and in paralytic ileus.

Para-amino Benzoic acid.(PABA): A crystalline powder, obtained from the yeast. It is sparingly soluble in water. This vitamin B component is concerned with the pigmentation of skin and acts as a catalysing agent for pantothenic acid, which is *antigrey hair factor*. Experimentally, grey hair has been produced by dietary deficiencies, and p-amino benzoic acid supplement, has not been able to improve it in human beings. It is also utilised as an essential metabolite by bacterial cells and thus can reverse the action of sulpha drugs by substrate competition. It is available as sodium salt, in *tablets* of 0.5 gm. *Initial dose:* 8 gm/o.s., *subsequent doses:* 2-3 gm/2-3 hrs. The effective blood concentration is 40 mg%. Its excretion is rapid and overdosages may give—(a) acidosis and (b) leucopenia. It was once used in the treatment of *rickettsial diseases*—typhus, rocky mountain and 'Q' fevers but after the discovery of antibiotics, this therapy is no more in use.

Biotin: A crystalline methyl-ester, which is present in liver and is synthesised in human intestine. Tumour tissues are 3 times richer in biotin and its deficiency causes dermatitis,

Choline and Methionine: *Lipotropic factor* and *amino acid*, respectively, which increase phospholipids and promote uses of fatty acids by the liver, thus controlling liver damage by the prevention of fatty infiltration. It is used in *cirrhosis of liver* and *hepatitis* Methionine 2 gm. for 7 days, followed by *choline dihydrogen citrate*—2 gm/OS for 3 months. It is also used in *icterus gravis*, *corneal scar* and *psoriasis*.

VITAMIN C

Ascorbic acid or vitamin C is perhaps the oldest vitamin known, its deficiency syndromes having already been observed, as early as 1564. It was first isolated by Szent Georgyi from the supererrenal bodies. It is widely distributed both in animal and vegetable kingdoms, the best dietary sources being citrus fruits and vegetables.

Orange juice	1 mg/ml.	Potatoes	12 mg/gm.
Rose hip	2 mg/ml.	Mother's milk	1 mg/ml.
Pine needles	1 mg/ml.		

It is also present in appreciable quantities in the amla powder and chillies. It is a simple carbohydrate ($C_6H_8O_6$), thermolabile and present in adrenal cortex and muscle tissues. It is stable in crystalline form and in acid solutions. Most of the animals synthesise it, excepting guinea pigs, monkeys and men, who get it from their foods.

Ascorbic acid is available in two forms l- and d-, the former being active. It is a powerful reducing agent, easily oxidised to 'dehydroascorbic acid', which reacts with glutathion, cystine and SH containing proteins, to reform ascorbic acid.

Unit: This is defined as the activity, contained in 0.05 mg. of l-ascorbic acid i.e. 20 unit mg. It is assayed *chemically* with dichlorophenol indophenol by titration method and also *biologically* in scorbutic guinea pigs. The *daily requirement* is 30-50 mg., the blood saturation amount is 1-2 mg.% and below 0.5 mg%, is the subnormal level. It is absorbed through gut and diarrhoea disturbs its absorption. It is excreted through urine.

Preparations: (a) Acid ascorbic 10, 25, 50, 100 mg. tabs/OS. (b) Na ascorbate—0.1, 0.5 and 1 gm/mg.

The optimum daily requirement is 50-75 mg. and the usual therapeutic dose is 100-200 mg/day. The commonly used proprietary preparations are *redoxon* and *celin*,

Actions: Vitamin C has an important role in the formation of intracellular substance in animal tissues. It helps in the formation of collagen fibres, which, along with ground substances and fibroblasts, carry out repair works in bones and cartilages, gums and wounds. It also helps in the formation of callous tissues. Dental decay may not be due to vitamin C deficiency but gum disorders are definitely due to this. Lack of intracellular material in blood vessels leads to subperiosteal haemorrhages. Vitamin C facilitates the production of matrix, impregnated with phosphatase and is thus essential for calcification. Ascorbic acid is required for growth and maturation of healthy red blood corpuscles and is also essential for the conversion of folic acid into folinic acid. Similarly, white blood corpuscles and platelets require ascorbic acid for their developments. It also takes part in the oxidation of l-tyrosine.

All these diverse actions may be mediated through the fundamental mechanism of *oxidation-reduction*, governing cellular respiration, vitamin C being a strong reducing agent. The deficiency of vitamin C also induces hyperglycaemia which is resistant to insulin injection. It plays a vital role in the detoxicating mechanism in the body, of metals, infections and other poisons. It stabilises suprarenal and other hormones and sometimes may even labilise them. Vitamin C stabilises adrenaline and insulin secretions and antagonises thyroxine.

Avitaminosis C: The typical deficiency syndrome is manifest in *scurvy*, with (a) sore and bleeding gums, decaying teeth, (b) fragility of capillaries, petechaeal haemorrhages, joint pains, muscle weakness, diarrhoea, oedema and enlarged heart. It is reproducible in guinea pigs in 120 days, when kept on scorbutogenic diets.

Hypovitaminosis: This is much more frequent these days than scurvy. It causes (a) night blindness, (b) skeletal and dental changes in children, (c) haemorrhagic tendencies and (d) microcytic anaemias.

On testing vitamin C content in urine, if it is found to be less than 15 mg/day and after a loading dose of 500 mg. of vitamin C, there is delayed and relatively small excretion, it is indicative of vitamin C deficiency, needing high doses of vitamin, for saturation in blood and tissues.

Uses: (a) Treatment of scurvy and all subdeficiency conditions.
(b) Infectious diseases, including tuberculosis.
(c) Anaemias.
(d) Detoxification of toxins.

- (e) Healing of wounds and fractures.
- (f) Preservative and stabiliser of pharmaceutical preparations.

In rickets and in metabolic strains of pregnancy, vitamin C supplement along with other vitamins, is specifically indicated.

SCOPE OF USE OF VITAMINS AT A GLANCE

<i>Pathological Conditions</i>	<i>Vitamins Indicated</i>
NIGHT BLINDNESS, OPTIC ATROPHY AND INTERSTITIAL KERATITIS; HYPERKERATOSIS AND XEROSIS; INFANTILE ECZEMA; GENITOURINARY & RECURRENT RESPIRATORY TRACT INFECTIONS AND RENAL CALCULI	
RICKETS, OSTEOMALACIA, OSTEOPOROSIS; SPASMOPHILIA AND TETANY: LEAD POISONING	D
PROLONGED CORTICOSTEROID THERAPY; HEALING OF FRACTURES; DENTAL CARIES	D, C
SCURVY, HAEMORRHAGIC DIATHESIS; NEONATAL HAEMORRHAGES; HEALING OF WOUNDS, INFECTIONS, PEPTIC ULCER; X-RAY THERAPY: RETARDATION OF GROWTH; ANAEMIAS IN GENERAL	C, B COMPLEX: FOLIC ACID AND B ₁₂ IN INDIVIDUAL TYPES
MUSCULAR DYSTROPHIES; MENTAL RETARDATION; CHRONIC MYOCARDIAL DISEASES	E
HAEMORRHAGE IN LIVER DISEASES.	P
HAEMORRHAGE FROM ANTICOAGULANT AND OTHER DRUGS	K
BERIBERI, PERIPHERAL NEURITIS, NEUROPATHIES, NEURALGIAS; DISEASES OF THE NERVOUS SYSTEM; ODEMAS OF CARDIAC ORIGIN	B ₁
ENCEPHALOPATHY AND DELIRIUM TREMENS	B ₁ , B ₂ , B ₆ , B ₁₂
CONVULSIVE DISORDERS	B ₆ , B
RADIATION SICKNESS	B ₁ , B ₂ , B ₆ , Pantothenic acid
GLOSSITIS, STOMATITIS AND CHEILOSIS	B ₂ , B ₆ , B ₁₂ , FOLIC ACID
HYPEREMESIS GRAVIDARUM	B ₆ , B ₁
PELLAGRA	NICOTINIC ACID, B ₂
MOTION SICKNESS AND MENIERE'S SYNDROME.	B COMPLEX NICOTINIC ACID

<i>Pathological Conditions</i>	<i>Vitamins Indicated</i>
SEBORRHOEIC DERMATITIS; SCROTAL, ANAL, PERINEAL PRURITIS AND ACNE.	RIBOFLAVIN, B ₂ , B ₆ , OR PYRDOXINE B ₁ , B ₂ .
PSYCHIC DISORDERS: IRRITABILITY, INSOMNIA, HEADACHE AND OTHER VAGUE TROUBLES.	NICOTINIC ACID, B ₆ , B ₁ , B ₂ .
BURNING FEET SYNDROME	PANTOTHENIC ACID, B ₆ .
AGRANULOCYTOSIS, REFRACTORY ANAEMIA ISONEX, DILANTIN, CURARE THERAPIES. ALOPECIA	B ₆ . CALCIUM PANTOTH- ENATE, B ₆ .
MALABSORPTION SYNDROME, FLATULENCE, DISTENSION, ACHLOR AND HYPOCHLORHY- DRIA.	B COMPLEX.
CONVALESCENCE, PREMATUREITY, PREGNANCY AND LACTATION, RETARDATION OF GROWTH, THYROTOXICOSIS, ACUTE INFECTIONS AND STRESS PROLONGED ANTIBIOTIC THERAPY.	B COMPLEX AND IN SOME CASES D ALSO.
VASCULAR DISORDERS AND HYPERCHOLESTEROLAEMIA, ATHEROSCLEROSIS, DIABETES. OPTIC ATROPHY, INTERSTITIAL KERATITIS.	NICOTINIC ACID, B ₁ , B ₂ , B ₆ and OTHER COM- PONENTS NICOTINIC ACID, B ₂ , B ₆ .

THERAPEUTIC CONSIDERATIONS

The planning of vitamin therapy in an exact manner in deficiency states, is not always very easy. The diagnosis of the precise deficiency, individually or in other conditions, is difficult and under the cover of a pronounced deficiency, quite often, multiple subdeficiencies occur. As a general rule, the need for vitamin therapy presupposes that preventive measures, with good and balanced diet, have failed and that the deficit having been of long duration, large quantities of vitamin, over prolonged periods, will be required.

The *water soluble vitamins* are excreted rapidly, necessitating repeated small doses. The *oral therapy* may not always be suitable in all cases and for them, parenteral therapy is to be used. The *fat soluble vitamins* may sometimes cause hypervitaminosis and quite often, *subclinical*

vitamin deficiencies may be responsible for aggravation or prolongation of an underlying disease. *Finally*, it should always be remembered that the role of vitamin is to improve the patients' condition and not meet with the basic nutritional needs of the patients.

Many vague complaints like malaise, soreness of muscles, gums anorexia, loss of weight, mild diarrhoea, constipation, sensation of fullness after meals, vague abdominal pain, precordial distress, lassitudes and insomnia may all be the symptoms of borderline nutritive failures. When the patient does not feel well and is unable to define exactly what is wrong in him, one may not be very wrong in thinking of some mild *multiple deficiency syndrome*, in such a patient.

Avitaminosis A: Night blindness, xerophthalmia, pilot's spots, hyperkeratosis, recurrent respiratory tract infection and proneness to develop renal stones are often caused or associated with *vitamin A* deficiency. *Minimum daily requirement* of vitamin A is 1500 I.U., *safe requirement* 2000-5000 I.U. and *therapeutic dose* 60,000 I.U. till the symptoms are fully ameliorated and subsequently, the safe requirements should continue.

Scurvy: This is characterised by debility, muscular weakness, anaemia, subcutaneous haemorrhages, bleeding gums, periosteal haematoma, joint pain, proneness to infection and delayed healing of wounds. Radiological features like scorbutic joint, sharp epiphyseal lines may also be found. The daily requirement is 75 mg. and the *therapeutic dose* is 100-200 mg. daily for about 10 days. Some of the special preparations of *redoxon*, *celin*, may also be used.

Rickets: Delayed dentition, softening of bones, ricketty rosary, Harrison's sulcus, bending of tibia, bossy head, nonclosure of fontanellae, bone deformities, pain and difficulty in walking, nervous irritability, enlargement of liver, are some of the characteristic features. The *child* has to be given additional feeds and carbohydrates are to be restricted. Cod liver oil, sunbath, use of mercury vapour lamp and U.V. radiation are helpful. The daily requirement of vitamin D is 400-500 I.U. and the *therapeutic dose* 600,000 I.U. I.M. twice a week, 5-10 injections. Sometimes, *adexoline* and *radioatoleun* are also used.

Beriberi: Fatigue, stiffening of legs, hyperaesthesia, muscle weakness, wrist and foot drop and even flaccid paralysis, are sometimes produced. In the *Wet form*, in addition to neurological damages, cardiac enlarge-

ment, dyspnoea, palpitation, tachycardia, systolic murmur, generalised oedema and well-marked E.C.G. changes may occur. *Wernick's encephalopathy* is characterised by headache, vomiting, nystagmus, ptosis, personality changes and coma. *Daily requirement* of vitamin B₁ is 1 mg-/day. *Therapeutic dose* 100 mg. daily, I.M., for a month, supplemented by B. complex vitamins. *Special preparations* are *Berin*, *Benerva*, *Betaxane* and many others.

Pellagra: Glossitis, gastrointestinal symptoms, symmetrically disposed dermatitis on the parts exposed to sunlight, with butterfly distribution on face, neck, hands dorsum of feet, neurasthenia, depression and dementia are observed. *Secondary pellagra* is more often associated with chronic diarrhoea and mal-absorption syndrome. *Daily requirement* of vitamins B-6 is 20 mg. *Therapeutic dose* of Nicotinic acid 50-100 mg/day, in peripheral vascular and coronary diseases.

Antihypercholesterolaemic dose is 1000-2000 mg. daily, orally. *Special preparations* of *Pelonin*, *niacinal*, *aluminium nicotinate*, may also be used.

CHAPTER

52

PHARMACOLOGY OF ENDOCRINES

GENERAL CONSIDERATIONS. PHYSIOCHEMICAL AND EXPERIMENTAL
BACKGROUNDS. INTER-RELATIONSHIP OF HORMONAL CONTROL OF
FUNCTIONS. DEFICIENCY AND HYPERSECRETION SYNDROMES.
HORMONE ANTAGONISTS

[Hormones are the natural secretions of the endocrine glands and these, together with autonomic nervous system, local hormones, enzymes and vitamins, act as chemical regulators of the intricate bodily functions. Besides, as they are also used as drugs, Dale has rightly designated them under the heading of *Autopharmacology*.

According to their *morphological* and *functional* characteristics, the hormones may be classified into *three* principal groups—(a) Purely endocrines, (b) Endo-exocrines and (c) Nonglandular endocrines. *Purely endocrines* are those whose functions are principally restricted to secretion, storage or release of the hormone. The *endo-exocrines* subserve a dual function. They secrete hormones in the blood stream and also an exocrine secretion through a duct e.g. pancreas. The *nonglandular endocrines* secrete hormone-like substances without subserving any exocrine function. The transmitters at adrenergic and cholinergic nerve endings and histamine, 5-HT etc, come under this group. *Chemically* hormones represent a very diverse group of compounds from the simple *aminoacid* derivatives like adrenaline and thyroxine or polypeptides to those which are *proteinous* in structure like pituitary, parathyroid and pancreatic hormones and also *steroid* hormones like corticosteroids and sex hormones.

The view that the anterior pituitary controls all the other peripheral endocrine glands, excluding the parathyroid and to some extent the pancreas, and that a suitable and exquisite reciprocal equilibrium between the concentrations of the circulating *peripheral hormones* and the quantities of the corresponding pituitary hormones exists, is not fully tenable. For the most part, the centre of the control of the adrenohypophyseal functions is to be found in the *hypothalamus*. The 'feed-back' relationship between the peripheral hormone levels and adreno-hypophyseal secretions, are transhypothalamic and that the hypothalamic control over the functions of the pituitary is exerted through the secretion of the hypothalamic hormones or releasing factors. They may be called hypophysiotropic substances or hormones.

Clinical conditions present in hyposecretion syndromes have the use of the same hormone, as *replacement therapy*, but the clinical conditions characterised by *hypersecretion* conditions do not yet have any appropriate drug, capable of antagonising or inhibiting their secretions, always. Direct inhibition of the action of hormone on its specific sites, has been achieved experimentally in several instances, as in antithyroid drugs.

Though some efforts have been made to isolate *antihormone substances* from the serum of experimental animals after injection of gradually increased doses of particular hormones, their clinical effectiveness as antagonists, have not yet been satisfactory, as an appropriate answer to the problem of hypersecretion conditions, for which, most of the medical treatment is still very defective, leaves the only alternative to surgical interventions and eradication therapy, which are also not highly successful. Therefore, search for clinically effective antagonists of normal regulatory interactions of the endocrine system, is still to be continued.]

These are the glands with internal secretions, which, along with the autonomic nervous system, local hormones, enzymes and vitamins, act as *chemical regulators* of various bodily functions. As they are the normal constituents of the body, as well as drugs, they have been named as *autopharmacology* by Dale.

Types: The endocrine glands can be classified into three principal groups depending upon their morphological and functional natures:

(a) *Purely endocrines*: or those whose functions are principally restricted to the secretion, storage or release of the hormone. (i) *Thyroid* is the storage type and (ii) *Parathyroid* the solid type.

(b) *Endo-exocrines*: that have the dual functions of secreting hormones in the blood stream and also an exocrine secretion which is eliminated through a duct e.g. pancreas and liver.

(c) *Non-glandular endocrines*: They secrete hormone like substances without subserving any exocrine function e.g. adrenergic and cholinergic nerves. Histamine is also produced in a similar manner. These are destroyed so quickly after secretion that they produce localised actions and are known as *local hormones*.

Historical: The use of organ extracts in the therapy of diseases dates back to the days of Eber's Papyrus, Aristotle (B.C. 384-322) and Pliny (23-79 A.D.)

Paracelsus (1493-1541) justified the use of these extracts and gave the slogan '*similia similibus curantur*', which means that a diseased organ is cured by the use of a similar organ. This gave the concept that the hormones were the best examples of the *substitution therapy*. Later, this therapy became quite popular and even upto 1765, various types of organ extracts were included in the list of official preparations.

The first endocrine preparation to be used was the dried *thyroid gland* but the real change in the old therapy came with the discovery of the blood circulation by Harvey in 1628. In 1775, Borden expressed his

views that every organ elaborated a specific substance which entered the blood and was useful to the organism. He also thought that after castration, the deficiency symptoms were probably due to the failure of some humoral substances produced by the sex glands.

The other major discovery came with the pioneer work of Addison (1857) who showed that the destruction of the adrenal cortex led to the condition known as *Addison's disease*. Effective cortical extracts were however, isolated in 1927 only.

Since these earlier days, numerous outstanding discoveries in the field of endocrine therapy, have changed the entire outlook of the deficiency syndromes, caused by the defective secretions of various endocrine glands. The work of Evans, Li, Simpson, Saley, Sayers, Banting and Best, Kendall, Abel, Houssay, Dunn, Hench, Doisy (Plate XLIII; Fig. 112-115) and many others, has opened a new horizon in the field of endocrinology. Recently, efforts are being made for finding out the structural nature of most of the hormones and also obtain them synthetically.

General Considerations: The coordinated activities of the various components of the living body are achieved by the complex regulatory mechanisms. There are *two* major devices for integrating these activities. They may be *nervous* or *chemical*, which by a series of delicate interplay of mutually favouring or opposing actions, regulate the ultimate cellular activities and maintain the constancy of the *milieu interieur*. Hormones are endogenously produced chemical substances which exercise profound effects on the cellular metabolism, mutually influencing each other's action. The regulatory functions of hormones differ from the controlling functions of the nervous system, in that, that the hormones are transported to the affected tissues by the blood. Some of the hormones affect nearly all the tissues of the body, while the action of others, is restricted to certain excitable tissues or organs. A group of chemical substances referred as *local hormones* e.g. acetylcholine, noradrenaline, 5HT, histamine, angiotensin, bradykinin, originate from the sites other than the well defined endocrine glands and are disposed after the local actions are produced.

The rates of production of most of the hormones are regulated normally by a *negative feed-back mechanism*. When a hormone performs and completes its target mission, its production is diminished or inhibited by the hormone itself or by the neurohumoral mechanism. In this way, *endocrine homoeostasis* is normally maintained.

Chemically, the hormones represent a very diverse group of compounds. Some of these like adrenaline and thyroxine are relatively

Plate XLIII

SOME PIONEER ENDOCRINOLOGISTS



FIG. 112. F.G. Banting



FIG. 113. E.C. Kendall



FIG. 114. P.S. Hench



FIG. 115. E.A. Doisy

simple types of amino acid derivatives. Several groups of hormones including those produced by the adrenal cortex and gonads, are *steroids* in nature, while the pituitary, parathyroid and the pancreatic hormones are polypeptide or *proteinous* nature. The molecular weight of the latter, ranges from about 1000 to 30000. As a result of the greatly improved methods of protein and amino acid isolation and characterisation, a number of nitrogen containing hormones have been obtained in highly purified forms and in some cases, complete amino acid sequences have also been determined.

In this manner, many hormones have been identified, isolated, purified and even synthesised. Although hormones have found a logical use as *replacement* or *substitution therapy* in such conditions where their deficiencies exist, they are also now being increasingly employed in the treatment of many other conditions even when the rationale of their uses, is still not clear. Many of the natural hormones suffer from various drawbacks when used in therapies. The protein hormones are not useful orally and many others like the sex hormones, have a very short duration of action. Increasing attempts are being made to synthesise derivatives which are devoid of these drawbacks. Besides the limitations inherent in all the substitution therapies, which mostly replenish the deficient secretions till the therapy is continued, there are also other factors which disturb the predictable functioning of the hormones in the therapies of diseases. The regulation of hormonal secretion depends upon the efficient *feed-back mechanism*. Most of the hormones have a *tropic* hormone secreted by another gland. This tropic hormone stimulates the specific hormone e.g. adrenocorticotrophic hormone secreting cortisone and at the same time, the specific hormone thus secreted also inhibits the production of the tropic hormone.

The situation thus is complex and no wonder therefore that the results of hormone therapies would vary from miraculous cures to utter failures. This may greatly be due to our insufficient knowledge of the complicated biochemical processes involved in hormone action and also because of the unstable and unsuitable dosage-forms of many of the preparations.

Regarding their *therapeutic uses*, a special point for consideration is that the normal secretions are regulated by the need of the body, while the exogenous administration of hormonal preparations, produce *fluctuating concentrations*, often higher than what is required by the system. This intrinsic drawback has to be kept in mind while using them for any prolonged therapeutic purposes. That is why when using cortisone, insulin and sex hormones, the *tapering* of the dose is neces-

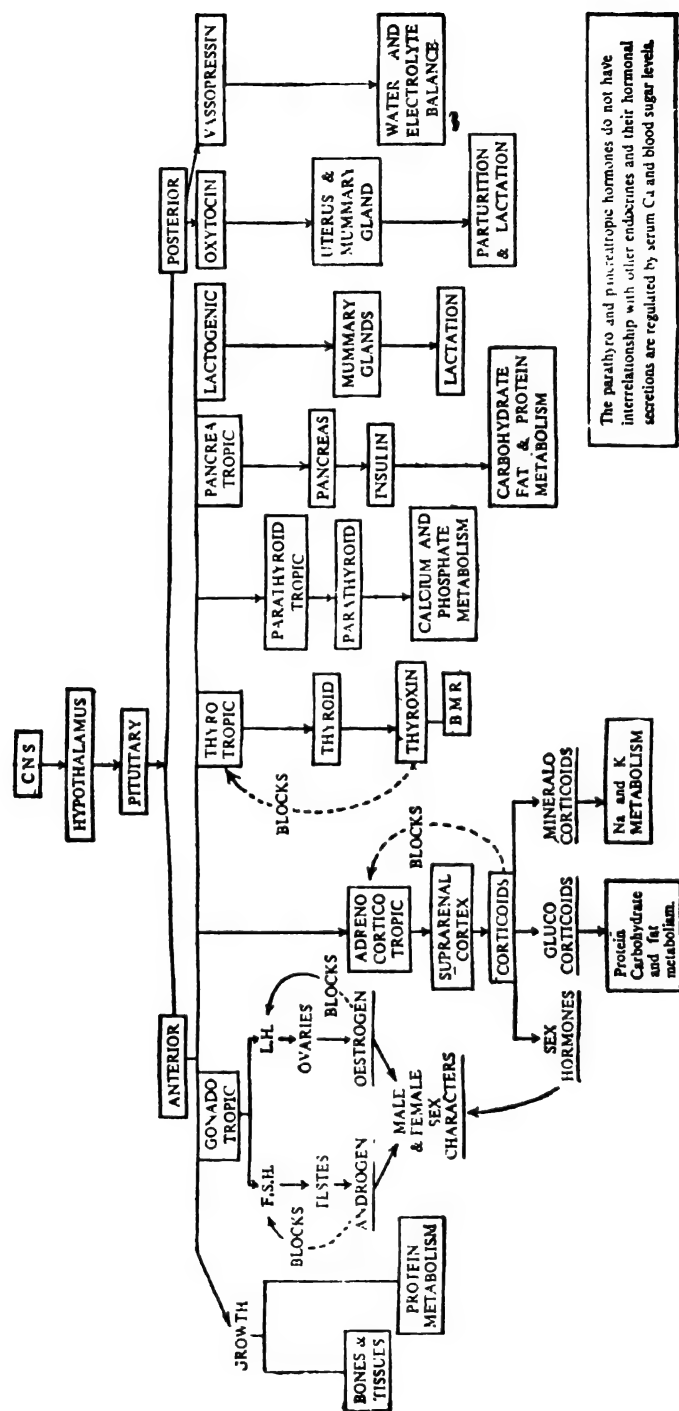
sary for permitting the endogenous secretion to adjust itself to the need of the system.

The other point for consideration is that with the advances in our knowledge, several of these hormones have found many other uses beyond their scope in the replacement therapy. For example, the *corticoids* are used not only in Addison's disease but also in allergic, collagen, infective and other conditions. Similarly, *female sex hormones* are used in male prostatic malignancy and *male sex hormones* in breast cancer. *Insulin* also finds many other uses, as in schizophrenia, hyperemesis gravidarum, acute alcoholism etc.

Inter-relation of Hormonal Control: In general, hormones have a regulatory action on the diverse metabolic effects of the body. It is characteristic of the endocrine system that a state of finely adjusted balance is maintained among the diversely acting endocrines, acting *sympiotically* or *antagonistically*, even in normal conditions. Furthermore, a reciprocal interaction not only exists but is also demonstrable, particularly in respect of the relationship of the anterior pituitary principles with various other glands which they affect. The way in which it controls the activity of other endocrine glands indicates that an *interdependance* of the glands exists. This is further substantiated by the fact that the complete or partial deficiency of one gland leads to a series of effects amounting to an increased or decreased activity of other glands. Similarly, the development of secondary sexual characters is controlled by several glands, e.g. not only the gonads and the adrenal cortex but the deficiency of thyroid and the anterior pituitary also causes an inhibition of the development of these characters. The interdependence does not only depend on the functional aspect of the problem but with advances of biochemistry and cellular chemistry, it is apparent that a network of changes is involved in producing an action which ultimately appears to be simple. This, in other words, is a type of chain-reaction which is going on in the system and therein lies the beauty of biological actions, which can adjust themselves in so many different ways, in cases of emergencies. This is shown in the *diagram* [Plate XLIII(a)].

Thyrotrophin controls iodine metabolism in the thyroid gland partly by regulating the iodide uptake and partly by regulating the formation of enzymes, involved in the various reactions of the conversion of iodotryosine to triiodothyrosine and thyroxine. The secretion of the pituitary thyrotrophin is regulated by the level of the blood thyroxine. It is stimulated by low blood thyroxine and inhibited by raised blood thyroxine levels. Normally, the activity of the pituitary and the thyroid

Plate XLIII(a)



Inter-relation of Hormonal Control

are finally integrated for maintaining an appropriate blood thyroxine level, with its resultant effect on the activities of the general tissues of the body.

The secretions of *ACTH* might be regulated by the blood level of the hormone formed by the gland on which it acts. A rise of blood corticoid level might inhibit the ACTH secretion by a direct action on the pituitary, while a fall in blood corticoids might increase ACTH secretion. Such a *pituitary-adrenal cortex-axis* would maintain a steady blood level of corticoids. Synthesis of corticoids under the influence of ACTH is very *rapid*, since the stores of the hormones in the adrenal cortex would last only for about 6 seconds, once the secretion has started. Chemical determination of cholesterol, the precursor of the corticoids and ascorbic acid, may be involved in the corticoid synthesis.

In several instances, it can be shown that the activity of the anterior pituitary is regulated by the blood level of hormones secreted by glands which are under its control. This mechanism is involved in the control of the secretion of thyrotrophin, gonadotrophin and also ACTH.

(a) Thyrotropin stimulates the secretion of thyroxine by the thyroid; the level of blood thyroxine in turn regulates the thyrotropin secretion, and increase in blood thyroxine depresses the release of thyrotropin, while a decrease of thyroxine stimulates its release. Both the pituitary and the thyroid glands form parts of a mutually interacting current, the activity of both being adjusted to maintain the normal state of the body. (b) The level of the blood oestrogen regulates the secretion of ISH. (c) the blood level of the adrenal corticoids may regulate the rate of secretion of ACTH. (d) Removal of thyroid, adrenals, ovaries or testes, produces histological changes in the anterior pituitary. (e) Testosterone, however, has little effect on the anterior pituitary.

The secretion of *aldosterone* is not controlled by the anterior pituitary, but by the concentration of electrolytes in the blood and by the blood volume. *Oxytocin* probably stimulates the release of the lactogenic and galactopoietic factors from the anterior pituitary.

Disturbances of the *growth* frequently accompany clinical disorders of the endocrine glands. Protein anabolism is favoured by the combined actions of the anterior pituitary growth hormone, thyroid hormones, insulin, androgens. Protein catabolism is favoured by the adrenal cortex.

The metabolism of *glucose* and other carbohydrates is controlled by a number of hormones secreted by different endocrines. The important ones are insulin, anterior pituitary hormones (ACTH, growth hormone and diabetogenic principle), adrenal cortex (cortisone and hydrocorti-

tisone), adrenaline, through the glycogenolysis and the activation of the phosphorylase, glucagon and the thyroid.

The metabolism of *fat* is controlled by a number of hormones either through the carbohydrate or the protein catabolism. The *thyroid* controls the serum lipids, notably the cholesterol level. The pituitary growth hormone causes a significant rise in the fatty acid level of the blood. This subsequently provides a source of energy in connection with protein anabolic effects of the growth hormone. The mobilisation of fat is controlled by the anterior pituitary and also by the adrenal cortex. Gonads have also been found to have influences on the levels of lipid and lipoproteins. Insulin brings about a decrease in the plasma level of fatty acids. This effect is opposed by adrenaline. The *mineral metabolism* is controlled by parathyroid, growth hormone, adrenal cortex, thyroid.

Antihormone and Hormone Antagonists: Clinical conditions, characterised by hypersecretion of hormones, have necessitated the search for drugs capable of antagonising or inhibiting their secretion. The substances of the former category are known as *antihormones*. These have been shown to be produced in the body after prolonged administration of certain *protein hormones* of the type of *thyroid extract*, particularly. They act like *antibodies*, because they are very specific in their effect. Those appearing in the blood of rabbits after the administration of FSH, are true antibodies, yielding the typical precipitin test. *Immunological methods* for hormone assay are being developed, which hold great promises. An assay method for the *parathyroid* hormone, has been developed utilising the quantitative complement *fixation technique*. This method is more precise than the bioassays and measures trace quantities of the hormone. In certain *Insulin-diabetic patients* the blood sera contains insulin neutralising antibodies. The experimental production of insulin immunological antibodies, is the basis of sensitive methods for insulin assay and also of experimental induction of insulin deficiency in animals. Antihormones, in spite of their promises, however, have still not found much therapeutic application, due to the inherent difficulties accompanying their isolation and also lack of knowledge.

The drugs of the *second* category i.e. those preventing the secretion of the hormones, have been found to be of much greater promise and it is now possible to inhibit thyroid and adrenal-cortex secretions, ovulation and many other functions. *Antithyroid* drugs inhibit the production of thyroxine by preventing the gland from incorporating inorganic iodine into the organic form. *Decreased aldosterone* activity

has been produced by *amphenone*, which depresses the aldosterone synthesis. More intimate knowledge about the mechanism of hormone secretion and its control, is destined to pave the path for the discovery of better drugs for hypersecretion syndromes, hitherto unknown.

ENDOCRINE SYNDROMES

	<i>'Name of endocrines</i>	<i>Hyposecretion syndrome</i>	<i>Hypersecretion syndrome</i>
PROTEINS	PITUITARY: (a) Anterior	Dwarfism, Simmond's disease.	Acromegaly, gigantism
	(b) Posterior	Diabetes insipidus	Cushing's disease.
	THYROID	Frohlich's syndrome	—
	PARATHYROID	Cretinism, myxedema	Exophthalmic goitre
	PANCREAS	Tetany	Osteitisfibros cystica
STEROIDS		Diabetes mellitus	Hyperinsulinism
	SUPRARENAL CORTEX	Addison's disease	Cushing' syndrome
			Cohn's syndrome or hyperadesteronism
	TESTES	Euruchoidism	
	OVARIES	Amenorrhoea	Metropathia haemorrhagica

Mode of Study: The functions of these glands can be studied either by animal experimentation or from the clinical syndromes presented by patients.

- (a) *Effects of extirpation*—Removal of a gland clearly establishes that it is of importance to the body, e.g. if before puberty, castration is done in the male, it leads to inhibition of the development of secondary sexual characters like growth of hair and creaking of voice. This then can be compared with the clinical syndromes, to pinpoint the effects of deficiencies.
- (b) *Effect of grafts and extracts*—The condition which results from the removal of the gland, is corrected by grafting the gland in question or by administration of the extract of the gland e.g. production of experimental diabetes by pancreactomy* and correcting it by a pancreatic graft or by the administration of insulin. This clearly establishes the role of the hormone in the pathogenesis of particular disease of hormonal origin.
- (c) *Isolation of hormones:* Isolation of the hormone from the gland and elucidation of its chemical nature e.g. hormones of anterior pituitary are proteins, while adrenal cortical hormones are steroids.

The methods of study and assay of hormones are diverse, depending upon the hormone concerned and the susceptible animal available for study. Though this will be discussed in the respective chapters, under the heading of *methods of evaluation* and also in the *chapter on bio-assay*, in a general way, it may be recapitulated that the *posterior pituitary* extract is studied on rat and guinea-pig virgin uterus, *ADH* on fowl B.P, *insulin* on rabbit blood sugar, with or without induction of alloxan diabetes. The hormones of *superarenal* glands are assayed on rats after ablation, the *thyroid* and *parathyroid* hormones on mice, rats, tadpoles and dogs, and *ovarian hormones* by different techniques on rats. For the *evaluation* of any of these hormones, the underlying principle is to produce deficiency syndromes in suitable animals and then to study their regression, after administration of extracts or active principles, which proves the underlying pathogenesis of the disorder.

From the foregoing, it is evident that the study of the hormones is not free from many difficulties, not only in respect of techniques of evaluation but also because of their multifaceted control mechanism and delicate chemical nature. Yet, their impact on therapeutics has been overshadowed by none, save probably, the antibiotics and chemotherapeutic agents.

CHAPTER

53

PHARMACOLOGY OF PROTEIN HORMONES

PITUITARY, THYROID, PARATHYROID AND PANCREATIC HORMONES. CHEMICAL NATURE, PHARMACOLOGICAL ACTIONS AND THERAPEUTIC STATUS

[Though the traditional concepts about the functioning of the *pituitary* as a *ring-leader* of the endocrine system has undergone some changes in the light of its working under the directives of hypothalamus and higher centres, there is no denying the fact that the pituitary with its large number of directly acting-growth, androgen and prolactin, as well as, the indirectly acting battery of tropic hormones, plays a major part in the control of the endocrine system. For its hypersecretion syndromes, there is at present, no therapeutic agent of any significance, whereas for the hyposecretion conditions, involving both growth, as well as gonads, replacement therapy with Antinutrin S or chorionic gonadotropin, is of some value. ACTH acts by stimulating the secretion of corticoids and finds its use in some of the conditions like gout, for which, the latter is also indicated.

The *parathyroids* are principally concerned with calcium metabolism. Its deficiencies lead to different types of tetany, for which, calcium and not parathormone therapy, is indicated. Parathormone is sometimes used as a deleading agent and in haemorrhages, resistant oedemas and hyperirritable states. Its hypersecretion, though rare, may result in hypercalcaemic disturbances, in which, serum calcium level goes beyond the normal level of 11 mg%.

Unlike parathyroids, the *thyroid* has many important functions—metabolic, growth, nutrition, diuretic and antitoxic, to perform. For this and for synthesis of thyroxin and triiodothyronine, iodine is an essential constituent and its metabolism in the body and the gland, shows remarkable selectivity in synthesis and storage. Thyroid disorders may be of congenital, acquired or of subthyroidism types. For cretinism and myxoedema, thyroid powder is mostly used and for thyrotoxicosis, antithyroid drugs and iodine preparations are effective. Important *anti-thyroid drugs* are—(a) Ionic inhibitors (b) Inhibitors of hormone synthesis and (c) Radiomimetic drugs. Of these, those mostly used are: (a) Lugol's as well as, radioactive iodine, (b) Thioamides and (c) Mercaptoimidazoles. For the medical care of thyrotoxicosis, bed rest, sedatives, propylthiouracil, mercazol and Lugol's iodine are used. Radioactive iodine is used in hyperthyroidism of elderly persons, threatening malignancies, resistant cases or cases with relapses. They are all toxic drugs and may give *side-effects* of iodism, agranulocytosis and sometimes myxoedema.

Since the discovery of *insulin*, much knowledge has been gained on normal and abnormal metabolisms of carbohydrates and the role of hormones in this, and in *diabetes mellitus*. The role of *insulin antagonists*, as also of HGF, in this respect, is also known.

Insulin is a complex polypeptide with 52 amino acids. It is available as crystalline, retard and lente forms. It acts on Krebs's and Meyerhoff's cycles facilitating the metabolism and utilisation of glucose at tissue levels. Its major use is in *diabetes mellitus*, for which, it is the drug of preference. It is also used in anorexia nervosum cyclic vomiting, hyperemesis gravidarum and in schizophrenia.

Oral antidiabetics are sulphonylurea and biguanide derivatives—tolbutamide or rastinon, chlorpropamide or diabenese, phenformin or DBI. They act by stimulating the secretion of insulin and are indicated in mild diabetes of elderly persons or in insulin resistant cases, in combination or otherwise, with insulin. They are contraindicated in juvenile diabetes and in hypoglycaemic states.]

ANTERIOR PITUITARY HORMONES

Historical: As the name implies, the pituitary was believed to be moistening the mucous membrane of the nose, till 1887 when Minkowski, for the first time, observed the association of acromegaly with a growth in the anterior pituitary lobe. It was only in 1900, that Hutchinson discovered the growth producing function of the gland and from the work of Evans and Long, the growth and gonadotropic roles of the anterior pituitary body, were established. Still later, by 1940, the work of Achner, Cushing, Smith and Ferguson, established the remaining functions of the endocrine, hitherto unknown. The isolation of these different fractions was considerably facilitated by the introduction of electrophoretic studies and the development of clinical endocrinology, further helped in our understanding their functions.

Physiological Considerations: The pituitary body, considered to be the 'ring-leader' of the endocrine system, consists of 2 distinct parts:

- (a) *Neural:* neurohypophysial—the posterior lobe.
- (b) *Glandular:* adenohypophysial—the anterior lobe.

From the standpoint of development and structure, they are markedly different and so also, functionally and hormonally.

The *first* has already been dealt with in the Chapter of *oxytocic drugs*. The *second* owes its origin to the *stomodeum* and *parsintermedia* is associated with it. *Adenohypophysis* contains *chromophobe* and *chromophil* cells (75% acido and eosinophils and 25% basophils). Their developmental interconversions may occur and this may also apply to the formation of the lactogenic hormone. The other pituitary hormones are secreted mostly by the basophilic cells.

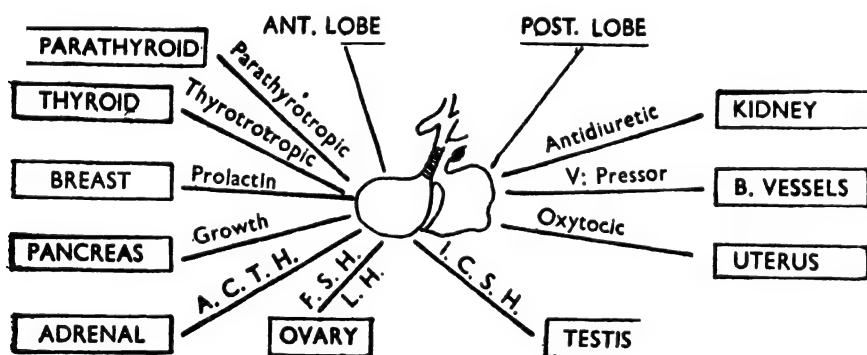
The human pituitary which weighs 4 gm. only and yields 1 gm. of dry powder, is an extremely complex body, elaborating a large number of hormones acting diversely and sometimes interpolating and controlling a large number of other hormones and hence known as *tropic* hormones. Being proteins, they cannot be isolated in pure form easily and therefore, our knowledge about the 'final interhormonal control' in the body, is still inadequate. However, there is no denying the fact that these complexities, strengthened by its vital role and wide control over other endocrines, entitles it to be the leader, of the 'endocrine system' in the body, to a great extent.

The anterior pituitary hormones, from their functional point of view, can be grouped under two heads:

(a) Self-sufficient and *directly acting* hormones: growth, androgens and prolactin.

(b) *Indirectly acting* members mediating their actions by stimulating the secretions of other endocrines: thyrotropic, parathyrotropic, gonadotropic and diabetogenic hormones.

The hormonal control of the pituitary is shown below:



Illustr. XXVIII. Schematic representation of the endocrine control of the Pituitary.

Hypopituitarism: This occurs from congenital anomaly, destruction or removal of the gland.

In adults, it may occasionally result from postpartum necrosis and the patient dies of adrenal deficiencies. Absence of lactation, alopecia, amenorrhoea, atrophy of genitalia, loss of libido, frequent episodes

of collapse and plumpism, are the characteristic tendencies. If treated with corticosteroids, thyroid and sex hormones, the replacement therapy leads to the clinical recovery.

In children, hypopituitary dwarfism is characterised by a lack of adeno-hypophyseal hormones. The child fails to grow in a global manner but the little growth that goes on, does not stop at puberty, thus eventually the stature may be all right. The thyroid and the adrenal cortex are also affected.

Hyperpituitarism results in *acromegaly* and *gigantism*, as detailed under growth hormone. Other hormones thyroid-adreno-cortical, prolactin and gonadotropin are also involved and precocious sexual development often occurs.

GROWTH HORMONE

A heat labile protein, obtained from the acidophilic cells of the anterior pituitary and is admixed with the gonadotropic hormone. Its excess or deficiency often affects the others also. The hormone is complex and shows special variations and specificities. It has been now isolated chemically and chromatographically and is present in the dry powder, to the extent of about 1 %. There are several variants.

Actions: Mainly anabolic affecting protein, fat, carbohydrate, enzyme and mineral metabolisms. Its stimulation results in the acceleration of growth, with gain in weight and its inhibition produces opposite effects. Rats are the most suitable animals for experimental studies.

Hypersecretion syndromes lead to '*gigantism*' or '*acromegaly*' according to the age of onset, with characteristic features and metabolic disorders.

Hyposecretion syndrome results in *pituitary dwarfism*, with sexual infantilism, girdle obesity, Lorrain-Levy and Froslich's syndrome (dystrophy-adiposus-genitalia), and '*pituitary cachexia*' (Simmond's disease). These disturbances are reproducible by experimental techniques, in rats and dogs. *Dose:* (a) Total extract—1 ml. (b) Antiurine growth—1 ml.

These preparations act only on parenteral administration and are not always useful in hypopituitary syndromes, for which, androgens, oestrogens, ACTH and thyroid preparations, are tried. Further, no exclusive growth hormone preparation is officially acceptable, at present as it is not available in absolutely purified form, free from the gonads.

GONADOTROPIC HORMONES

They stimulate gonads, increase the output of sex hormone and indirectly affect secondary sexual characters. In other words, they make the anterior pituitary act almost like a *time-keeper*, for regulating the sexual cycle in the females. There are four types of gonadotrophins as recognised entities, of which, two are of pituitary and two of placental origin-FSH, ISH, chorionic and pregnant mare's serum gonadotropins. They are all glycoproteins of 25,000-30,000 mol. weight.

Follicle Stimulating Hormone (FSH): It is secreted by the basophil cells of the anterior pituitary body and causes (a) development of graffian follicles and release of oestradiol in females. (b) Formation of the seminiferous tubules and also spermatogenesis in males. Though these have been experimentally proved, by ablation techniques, it may be remembered that deficiencies of other hormones are also induced, as selective ablation is not possible.

Luteinising Hormone (L.H. or I.C.H.S.): It helps in the formation of *corpus luteum* and then release of progesterone in females and testosterone in males. These two hormones are also responsible for the *Aschem-Zondeck* pregnancy test, carried out in rats, for early diagnosis of pregnancy.

Chorionic Gonadotrophin: It is secreted by the chorionic villi and is usually obtained from the urine of pregnant females. It is mainly luteinising in action but it also stimulates the testis and helps in its descent into scrotum. It is of use in *cryptorchidism* and is also tried in 'ovarian hypofunction', sterility and menstrual disorders.

Equine Gonadotrophin: It is obtained from the serum of pregnant mares and can be had in highly purified form. It possesses both follicle stimulating and luteinising actions. It has a prolonged effect, due to its slow metabolism. It is used parenterally in 'hypoovarianism'.

Metabolism: All these four hormones undergo enzymatic destruction in the G.I. tract and both endogenous, as well as, exogenous hormones are degraded in the body and not excreted, excepting the chorionic form. They have roughly a half life of 1 hour only, but in the case of chorionic gonadotrophin, it is of several hours duration.

Assay: This is carried out for F.S.H. from the increase in the weight of the ovary of immature mice and for L.S. from the increase in the weight of the prostate, in hypophysectomised immature rats.

Preparations: Chorionic gonadotropin or *Antuitrin S* representing 15,000 I.U. per mg. of powder, from which the growth hormone has already been removed. It is made into solution in sterile saline, in a strength of 1 in 1000-2000 I.U. and given I.M., twice or thrice a week, a course lasting for about 3 months.

Uses: (a) *Infertility*—due to defects in ovulation.

(b) *Cryptorchidism*—Chorionic gonadotropin—1000 to 2000 I.U., twice a week I.M. till descent of the testes.

(c) *Hyposecretion syndrome*—of dystrophy adipose genitalia. Fairly good result, if the therapy is started in correct time, with minimum effective doses.

PROLACTIN

It is a lactogenic hormone which initiates and supports lactation after the mammary glands have been suitably prepared by oestradiol and progesterone. Though it has been obtained in crystalline forms, it is not yet readily available for therapeutic uses.

ADRENO-CORTICOTROPIC HORMONE (ACTH)

It is also a protein hormone of the anterior pituitary body, a polypeptide of large molecular size, comprising of *alpha* and *beta* corticotrophins, isolated by paper chromatographic and electrophoretic studies.

Being a protein, it is thermolabile and readily destroyed by proteolytic enzymes of the stomach. On parenteral administration, it disappears from blood rapidly and produces its characteristic effects through the suprarenal cortex. Its action therefore grossly resembles that of 'corticosteroids'. Most of the drug is metabolised in the body and only a negligible quantity excreted in urine. *Corticotropin*—20, 40 units/ml. I.M.; *Repository form* in 15% gelatin. *Initial dose*, not exceeding 10-25 units. Its uses are the same as for corticosteroids and is detailed in that chapter.

The other *tropic hormones*—thyrotropic, parathyrotropic, diabotogenic, also act through their respective glands and will be studied in their appropriate chapters.

PARATHYROID HORMONE

In the challenging race for advancement in endocrinology, much progress has been made in recent decades. Though our knowledge about thyroid and antithyroid drugs has much advanced, the parathy-

roids however continue as weak links, with limited pharmacological and therapeutic possibilities.

The parathyroids were discovered at the end of 19th century, by Sandstörn and Gley. Their role in 'calcium metabolism' was established in 1909 by MacCollum and finally, the 'crude active principle' was isolated by Collip in 1925. Though *parathormone* has been obtained in a purified form, its exact chemistry is not known. It is protein in nature and is inactivated by acids, alkalies and trypsin. The hormone subserves *two important functions* (a) Regulation of calcium metabolism and (b) Detoxification of metabolic poisons. Of these, only the former is well established.

Calcium Metabolism: Parathormone maintains a constant calcium ion concentration in extra cellular fluids, by regulating its absorption, deposition, mobilisation and excretion. According to the Albrecht school of workers, it primarily induces *hyperphosphaturia* producing *hypophosphataemia*, which elicits *hypercalcaemia* with consequent *hypercalcaemia*. The net result of this is *enhanced excretion* of CaPO_4 . The above action depends on the blood calcium level and hypocalcaemia acts as a specific stimulus for parathyroid activity.

Hyperparathyroidism: It may result from an adenoma of the gland or from high dosages of parathormone. The *acute condition* is characterised by hypercalcaemia, diuresis, phosphaturia, anuria and later, renal failure. Besides these, anorexia, vomiting and muscular atony also occur. *Chronic hyperparathyroidism* is characterised by decalcification, cyst formation and fractures of bones, for which, surgical treatment is indicated.

Hypoparathyroidism: It is usually postoperative and may be in the form of *latent or manifest tetany*. If of *subclinical or chronic type*, the symptoms refer to the *ectodermal tissues*, mostly with loss of hair, brittle and grooved nails and cataract.

Besides hypoparathyroid tetany, there are also *other types of tetany* e.g. (a) the *alkalotic type*, which is due to the excessive vomiting (b) the *eucalcaemic tetany*, which results from gastric disorders and hyperventilation.

Preparations: Dessicated powder: 3-6 mg./os Parathyroid extract: 100 units/ml. 0.5-1 ml.

Collip's unit represents 1/100th the amount of parathyroid, necessary for raising blood Ca in dogs, by 1 mg.%, within 16 to 18 hours, after S. C. injection.

Uses: Better with discretion, as it is not free from danger. Attention to serum calcium level and hospitalisation of patients, are essential. The important uses are:

(a) *Tetany*: manifest type with characteristic carpopedal spasm, hypocalcaemia etc. *Calcium gluconate* is used I.V. for immediate effect, followed by parathyroid solution 0.5—1 ml. S.C. or I.M., for sustained action. When the acute stage is under control, low PO_4 but high Ca diet, *dihydratichysterol*—5 mg/ml or *vitamin D*, for elevating the serum calcium level, are recommended.

(b) *Alkalotic and eucalcaemic tetany*: Uses of ammonium chloride, calcium gluconate vitamin D and no parathyroid therapy, are the rules.

(c) As *deleading agent*, along with EDTA, with apparent good results.

(d) In *haemorrhage*, *resistant oedema* and as a sedative in hyperirritable conditions, its rationale of use, is not known.

THYROID HORMONES

Historical: The chapter is both old and new and full of many new discoveries:

(a) The gland was discovered by Wharton in 1656 and the presence of iodine detected by Courtois in 1811.

(b) The hypofunction state of myxoedema and its metabolic roles were discovered by Gall, Ord and Magnus, between 1874-95 and the glycerine extract brought into use by Murray, in hypothyroid states, in 1891.

(c) Crystalline thyroxine was isolated by Kendall in 1914 and the presence of iodine molecule established.

(d) The hormone was synthesised by Harrington and Barger in 1927, which remained unchallenged till tri-iodothyronine was isolated and synthesised by Leblond, Gross and Pitt Rivers, between 1951 and 1953.

Physiological Considerations: It is an important endocrine which is implicated in many important and intricate physiological and enzymatic functions, detailed hereafter:

(a) *Increased combustion and temperature regulation*: The basic metabolic rate is elevated and fat, protein and carbohydrate utilisation and tissue oxidation, enhanced.

(b) *Growth and nutrition*: are greatly facilitated and nutrition of

hair and nail improved. The metamorphosis of tadpoles to the frog stage, is quickened.

(c) *Diuretic action*: Excretion of H_2O , urea and chlorides is increased. It is an extra-renal diuretic in 'myxoedematous conditions'.

(d) *Sensitivity to poisons*: is enhanced. There is increased tissue permeability and greater diffusion of poisons into cells, during thyroid therapy.

Biochemical Considerations: In life, 1-2 gm. of iodine or 1/20 mg./day, is required. Thyroid contains 15 mg. of iodine, 65% of which is present in thyroxine. Iodine is present in both *organic* and *inorganic forms*, combined with amino acids and incorporated in colloids, as 'thyroglobulin', which is a large protein of 675,000 molecular weight.

Thyroxine was the accepted hormone for over 4 decades but in view of its less calorogenic activity, further work with radio active iodine and two dimensional chromatography, has revealed the presence of *tri-iodothyronine*, in thyroid and blood and this is now considered to be the real thyroid hormone, instead of thyroxine. It is an iodinated derivative of tyrosine, 5 times more potent than thyroxine and acts as a competitive inhibitor of the latter, on peripheral effector systems.

Chemically, 'thyroxine', 'di-iodotyrosine' and 'tri-iodothyronine' are fairly similar, di-iodotyrosine appearing to be an intermediate, in the synthesis of the above two.

Thyroxine is present in *levo*- and *dextro*-forms in the gland. In their structure-activity-relationship, the nature and position of halogens, phenolic CH, ether linkage, alanine side-chain, all appear to be important.

The glandular synthesis of thyroxine is not definitely settled as yet. Thyroid disturbances may occur from its abnormal synthesis, storage or release. Essential points in the synthesis and release of the hormone, are:

- (a) *Food iodine*, in elemental or ionic form, reaches the circulation and is quickly trapped by thyroid and oxidised into iodides by *cytochrome oxidase* and *peroxidase systems*. It is then incorporated in *tyrosine* to form *diiodotyrosine* and 3 mono-iodotyrosines.
- (b) The two *iodotyrosines* are joined together by *oxidative coupling*, with the loss of alanine side-chain, to form thyroxine and triiodothyronine. It is then bound with the protein and stored in the form of protein thyroglobulin.

Plate XLIV

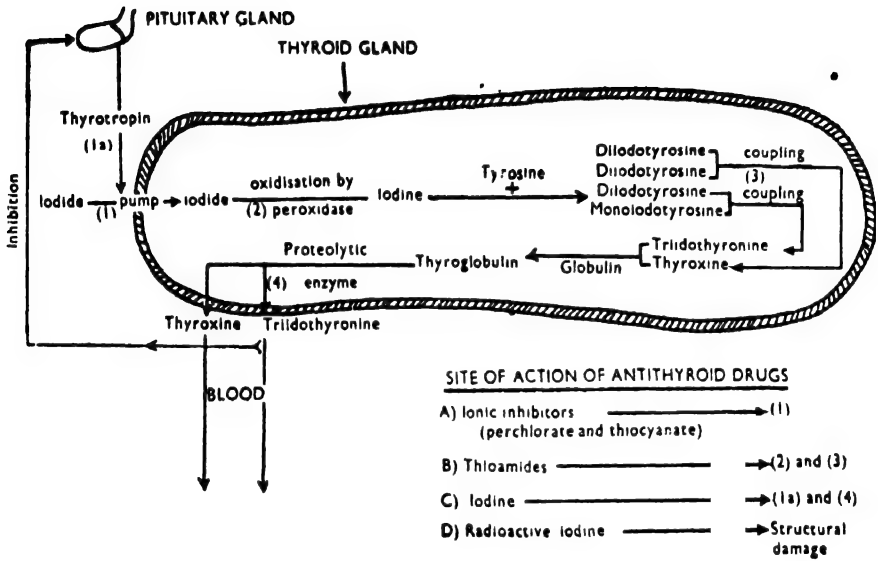


FIG. 116 Mechanism of synthesis and secretion thyroid hormones and site of action of antithyroid drugs.

- (c) *Thyroxine* and 3,5,3—*triiodothyronine*, are released under the influence of the proteolytic enzyme and passed into circulation.
- (d) The synthesis and release of the hormone is controlled by the thyrotropic hormone of the anterior pituitary gland.
- (e) There is an activation of this process in thyrotoxicosis with increased blood iodine content.

Thyroid-Pituitary Interrelationship: Thyroid activity is regulated by anterior pituitary (Plate XLIV, Fig. 116) through the specific hormone—*thyrotropine*, the rate of secretion of which, is delicately controlled by:

- (a) The quantity of the circulating hormone, being depressed by an excess and increased by a deficiency, of tri-iodothyronine.
- (b) Hypothalamus, through a neurohormone and cold environment, activates its secretion, while heat depresses the same.
- (c) Dietary deficiencies, stress, general ill-health and certain drugs, also probably mediate their actions on the thyroid, through the hypothalamus.
- (d) *Thyrotropine* or TSH, in experimental animals, produces a number of changes (a) increased thyroid hormonal secretion, (b) increased vascularity of the gland, (c) enlargement of thyroid cells and reabsorption of colloids and (d) enhanced uptake of iodine by the glands. In iodine deficiency, there is increased secretion of thyrotropin, with compensatory hyperplasia of the gland, increased vascularity and also enlargement.

Hypothyroidism: It may manifest itself in *three* different forms:

(a) *Congenital deficiency: Cretinism* with stunted growth, both mental and physical, stunted sexual development, adenoids and susceptibility to infections. This is improved by 'thyroid therapy'.

(b) *Acquired deficiency: Myxoedema* with '4 Fs'—fat, fair, flabby and flatulent, the patient is a pathetic, pigskinned, with alopecia and oedematous appearance, a toad-like caricature of the human race, as aptly stated by Osler. This is also improved by thyroid therapy.

(c) *Subthyroid states:* with skin, nail and hair troubles, cold hands and feet, constipation, scanty menstruation and obesity. This is also improved by thyroid medication.

Hyperthyroidism: In this, there is both hypertrophy and hyperplasia of the gland, mediated through thyrotropic hormone, as well as iodine

deficiency. Histological changes in the gland comprise transformation of cuboidal to columnar cells, with increase in the number of follicles. Both colloid and iodine contents are reduced. The gland initially acts under stress without any deficiency in hormone synthesis, resulting in the formation of simple goitre. If iodine deficiency is remedied at this stage, the gland may involute, be filled up with colloids and histological changes return to the normality. If this does not occur, the goitre changes to thyrotoxicosis with the symptom complex of anxiety, insomnia, palpitation, perspiration, exophthalmos and a raised B.M.R. There is hyperplasia with relative iodine deficiency, increased hormonal secretion and pituitary, as well as, sympathetic disturbances, underlying the condition. It is improved by *iodine* and *antithyroid drugs* and not by thyroid hormone.

Preparations: (a) *Thyroid powder*—standardised to contain 0.1% of iodine and 1 mg. of thyroxine in 0.6 gm. of the powder. *Tablets:* 15, 30, 60 and 120 mg.-plain or enteric coated.

(b) *Sodium laevothyroxine:* 0.1-1 mg., as 0.05, 0.1, 0.2 mg. *tablets.*

(c) *Sodium liothyronine:* *Tablets* of 5 and 25 mg. Though quicker in action, it is not suitable for any prolonged use.

Assay: 1. *Chemical* by estimation of *total inorganic and organic iodines.*

2. *Biological* (a) from the rate of metamorphosis of the *tadpole*, as compared to that of the standard.

(b) from comparison of *metabolic rate* in mice from the ratio of O_2 consumed/ CO_2 exhaled after ST and T.

Metabolism (a) The thyroid presents a rare example of satisfactory *oral use* of a protein hormone though absorption and utilisation are slow.

(b) O_2 utilisation is increased by 40% from its action on the cytochrome-oxidase system, each mg. of thyroxine increasing B.M.R. by 2%.

(c) In case of tri-iodothyronine, it is even more.

(d) It has an equally slow excretion, mostly in faeces, about 1/20 per day and confirmed by 'labelled thyroxine' studies.

Toxicology: This is due to drug *cumulation* and occurs after weeks of therapy. The symptoms are those of *thyrotoxicosis*. Its management implies—cessation of therapy, administration of 'lugol's iodine' and sedatives.

Uses: 1. *Major indication* of thyroid therapy is only one (a) *thyroid deficiency states*, as occur in (i) *Cretinism* (ii) *Myxoedema*. (b) *Subthy-*

roid states, the first is congenital and occurs in early childhood and the second and the third are mostly acquired. (c) With early and carefully planned therapy, in gradually increasing and decreasing doses and adequate vigilance about *cumulative toxicity*, the 'aphorism of Osler'—that even the magic wand of Prospero could not produce such results, may be expected, to a great extent.

2 *Minor Uses*: (a) *Obesity* (b) *Skin diseases*—psoriasis, eczema and frostbite (c) *Diuretic* in subthyroid states only (d) *Mental deficiencies*, (e) *Chronic rheumatism* (f) *Chronic constipation*—doubtful result. In any of these conditions, thyroid will act only if there is some 'subthyroid state'.

THERAPEUTIC DETAILS

Myxoedema: Usually dry powder or in tablets form is prescribed, the average, daily dose being 120-180 mg. A full replacement dose is necessary for young patients and adults. In older persons with heart conditions—the initial dose is 60 mg/day for 2 weeks, gradually increased to 180 mg/day.

Cretinism: It needs careful thyroid therapy in a dosage schedule indicated below:

<i>Age</i>	<i>Dosage per day of powder</i>	<i>Age</i>	<i>Dosage per day of powder</i>
2- 4 months	6 mg.	12-26 months	24-45 mg.
4- 8 months	12 mg.	2- 4 years	30-90 mg.
8-12 months	18 mg.	4-12 years	60-100 mg.

The success of treatment depends upon the time of onset of the therapy, the best result being expected if the therapy is started at the earliest, indication after birth. The treatment is started with 15 mg/day for the first few months and increased to 45 mg./day at the age of 14 months. Some physical and mental development can be expected in this condition. Untoward effects of hyperthyroidism are palpitation, cardiac pain and muscle cramps and may necessitate immediate cessation of therapy and treatment with iodine and antithyroid drugs.

Simple Goitre: This is due to the excessive thyrotropic stimulation from deficient thyroid hormones and consequently, full replacement therapy with thyroid in *full doses* of 150 mg/day, to suppress T.S.H. is advisable. *Prophylactic and palliative iodine therapy* is also advocated.

THYROIDOMIMETIC AND GOITROGENIC AGENTS

Dinitrophenol: Another stimulant of metabolism like thyroid, which, in a dose of 3-5 mg/kg. raises B.M.R. by 20%. The drug increases O_2 consumption by stimulating the combustion of fats. It is a highly toxic substance and produces gastric upset, cyanosis and profuse perspiration. It is not of any therapeutic use.

Goitrogenic Agents: These are the agents which prevent or diminish the biosynthesis of thyroid hormone and cause an enlargement of the gland. They may be of *synthetic* or *plant* origin. *Synthetic agents* are the antithyroid drugs. *Goitrogenic agents of plant origin* include cabbage, rape and mustard seeds, which contain 1-5 vinyl-2 thiooxazolidone and have been found to produce goitre in animals.

ANTITHYROID DRUGS

These are a group of old and new drugs which depress excessive thyroid activity in *thyrotoxicosis* and other *hyperthyroid states* by diverse mechanisms, acting at different strategic points, pertaining to synthesis, release or peripheral actions of the hormone, detailed hereafter. They are all, more or less, toxic and have to be used with appropriate caution.

CLASSIFICATION

'IONIC INHIBITORS' PREVENTING COLLECTION OF IODIDES IN THE GLAND	Thiocyanate, perchlorate, nitrate fluoro sulphonate, difluorophosphate.
INHIBITORS OF HORMONE SYNTHESIS	(a) Iodides (b) Thioamides (i) <i>Thiourea derivatives</i> :— thiouracil, methyl and propyl thiouracil, iturmil. (ii) <i>Mercaptoimidazoles</i> :— mercazole, neomercazol and methimazole.
THYROID INHIBITOR BY TISSUE DESTRUCTION	(a) Radioactive iodine (b) X-rays.
MISCELLANEOUS INHIBITORS	(a) Sulphonamides and PAS (b) Resorcinol and Fluoroglucinol (c) Thiobarbital, aminothiazol, cyanamide, amphenon B, cobaltous ion, carbutamide.

IONIC INHIBITORS

Being anions, resembling iodide ions, they interfere with the concentration of iodide ions by the gland, as competitive inhibitors.

Thiocyanate: It prevents the incorporation and oxidation of 'I' in the hormones. It has inhibitory effect on the iodide binding also. It is metabolised in the gland and because of toxicity, it is not used in therapeutics.

Perchlorate: It resembles thiocyanate in action but has no effect on the binding of iodine. It disturbs the trapping and utilisation of iodine. It is concentrated in the gland and is not metabolised. Na and K salts were in use in the past, but due to their extensive side-effects: gastric irritation, fever, skin rashes, lymphadenopathy, agranulocytosis and aplastic anaemia, their use is now limited to the refractory cases only. *Dose:* 800-1000 mg/day.

IODINE

The remarkable, temporary palliative effect of iodine in hyperthyroidism, has long been known. It is paradoxical, because iodine is essential for hormone synthesis and prevention of endemic goitre. The rationale is that in all these conditions, there is relative iodine deficiency and hence its beneficial effect.

The usual treatment comprises the use of 5-10 drops of *Lugol's iodine* t.d.s. The symptoms of hyperthyroidism—sweating, tremor, tachycardia and increased B.M.R., all disappear. The gland regresses, becomes less vascular and suitable for surgical measures. The improvement may start in a day or two and is complete in 10-14 days but is usually followed by a relapse.

Mode of Action: Though the exact mechanism is not fully known, it may be due to some of the following:

- (a) Inactivation of proteolytic enzymes, disturbing hormonal release.
- (b) Inhibition of T.S.H., producing glandular atrophy and
- (c) Inactivation of oxidative enzyme by the excess of iodine therapy, affecting hormone synthesis.

Preparation: *Lugol's iodine* (iodine 5% + KI 10% in H₂O *Dose:* 0.3-1 ml. Iodine is reduced to iodide in the intestine before absorption.

Uses: (a) *Thyrotoxicosis*: The antithyroid action is temporary as the stored hormone in the gland spills over into the blood, producing exacerbation of symptoms, which is known as *escape phenomenon*. Further, the use of Lugol's iodine in hyperthyroidism is limited by the toxic effects of *Iodism*, comprising rashes, swelling of salivary glands, coryza and flaring up of gummatous lesions, if present.

(b) *Endemic Goitre*: 0.1 mg. of iodine in 10 gm. of table salt or Lugol's iodine 1.3 ml/week.

RADIOACTIVE IODINE

The different *isotopes*: I^{130} , and I^{128} , with their *half lives* of 12.6 hours, 8 days and 60 days, respectively, are used for biological studies and therapeutic applications. I^{131} emitting *beta* and *gamma* rays, providing ionising radiation for 90 % destruction of tissues, has already been dealt with in the *Chapter of Isotopes*.

Radio iodine is obtained by the nuclear bombardment of tellurium in the presence of KI and H_2SO_4 or by the fission of uranium. I^{131} retains only 10 % of activity at the end of a month. It is used both for diagnostic, as well as, *therapeutic purposes*, in a dose of 25-30 mc/3 months.

When radioactive NaI is given by mouth, the uptake of iodine by the thyroid gland can be measured by the *Geiger-Müller counter*, by counting the gamma rays. The thyroid of a normal person takes up only 30 % of the dose but in toxic goitre, this may be as high as 70 %.

The therapeutic uses of I^{131} , rest on the selective concentration of iodine by thyroid. The isotope is incorporated in Iodoamino-acids, deposited in the colloid of the follicles and it then emits ionising beta rays, which interfere with mitosis and destroys proliferative tissues. Its effects on other body tissues are minimum. NaI solutions for oral and I.V.:—5-15 mc/10 ml.; 15-40 mc/20 ml. upto 250 and 1000 mc/10 ml. concentration, are available. About 50-66 % of patients improve from a *single dose* and another 20 % after a *second dose*. The remaining may need a *third dose*. The advantages of the treatment are that no hospitalisation, no risk, no discomfort, no other tissue damage and no relapses are often observed.

Indications: (a) *Malignant and inoperable cases* of thyrotoxicosis, in older people and with heart diseases.

(b) *Frequently relapsing cases*, resistant to other drugs and also *nodular goitres*.

(c) *Angina* and *C.C.F. cases* for reducing the O_2 need of the body.

Dose: proportional to the iodine uptake viz. 25 mc if 70%; 50 mc. if 20%. The dose is repeated after 3 months. The result of the above therapy is not dependable.

- (d) **Diagnostic uses** (i) Hyperthyroidism and myxoedema, (ii) Thyroxine metabolism (iii) Ectopic thyroid tissues, (iv) Causes of simple goitre.

Limitations: These are the following:

- (a) Inadequate concentration of the isotope in cases of carcinoma of the gland.
- (b) Radiation hazards: sickness, agranulocytosis and higher incidence of myxoedema.
- (c) Though dramatic result in selected cases of malignancy, it cannot be fully exploited because of the short life and nonavailability of the drug.
- (d) The therapy needs long time, sometimes months together, before the patient is well.
- (e) It is not used in children for the risk of myxoedema and also, not during pregnancy.

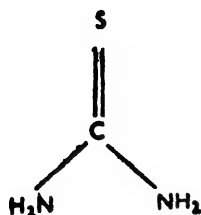
SYNTHETIC THIOAMIDES

These, comprising mostly of *thioures* and *imidazole* derivatives, along with radio-active iodine, have greatly revolutionised the therapy of thyrotoxicosis, in recent years. They have *specific antithyroid activity*, with special references to the inhibition of hormone synthesis, as revealed by the work of Maekenzie (1941), Krantz (1942), Astwood (1943).

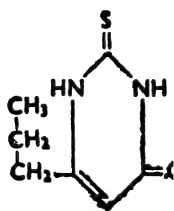
Thiourea derivatives are crystalline in nature and marketed in *tablet forms*, their dosages varying with their relative potency: *thiourea*-3 gms., *thioureacil*-250 mg., *methythyouracil*-100 mg., as initial loading dose/day, the maintenance dose being about 1/4th of this.

All of them are readily absorbed, uniformly distributed and excreted in urine. Their therapeutic use is limited by their blood toxicity. *Thiourea* and *thioureacil* produce a number of alarming *allergic* manifestations and the former, also an unpleasant odour in the breath. *Thiouracil* also causes a dangerous *agranulocytosis* and death, for which, its uses have almost been abandoned.

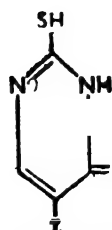
Chemistry: The chemical structure of different groups of synthetic antithyroid agents are given below;



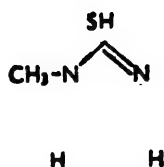
THIOUREA



PROPYL THIOURACIL



ITRUMIL



MERCAZOLE

It will be seen from the above that thiourea and heterocyclic compounds containing a thiouracil group, form the majority of important antithyroid agents. Among the heterocyclic compounds, it will further be observed that the *imidazole*, *oxazol*, *hydantoin*, *thiazole*, *uracil* and *barbituric acid* derivatives are the important ones. *Methylthiouracil* has been used in doses of 50-100 mg/thrice a day, but it has the same limitations as the other two compounds, in this series.

PROPYL THIOURACIL

This is a compound of much greater therapeutic value than thiourea itself. It is less toxic, sparingly soluble and frequently used. The action is prompt and durable. *Tablets*: 50 mg., initially, 100-200 mg. in divided doses/day, gradually raised to 350 mg/day, are recommended for use. It has a brief duration of action. It *inhibits thyroxine* secretion and this may lead to hyperplasia, increased vascularity and enlargement of the gland from overactivity of thyrotropin. *Methyl thiouracil*, though more potent, is more toxic and if used, the *dose* is 50 mg. tablet q.d.s.

ITRUMIL

5-iodothiouracil, containing 46% of iodine in organic combination, in the body, it probably yields both iodine and thiouracil effects. It has been used in the preoperative preparation of the patients and has been claimed to depress T.S.H. and thus not enlarge the thyroid. *Dose*: Itrumil sodium-150-300 mg/day or less, in the form of 50 mg. tablets. On the whole, the clinical reports have not fully substantiated the claims of advantages made.

MERCAZOLE

Also known as *tapazole* or methimazole, is a methyl mercaptoimadazole derivative. It is 25 times more potent and less toxic than thiouracil. *Dose*: 6-10 mg./day, for 2 weeks and 1 mg./day, thereafter.

NEOMERCAZOLE

This has the strongest antithyroid activity and is 40 times more potent than thiouracil and 10 times stronger than propyl thiouracil. It however, produces dangerous *bone marrow aplasia* and *agranulocytosis*. *Dose*: 5-10 mg. t.d.s.

Mechanism: and Actions: (a) All these drugs are satisfactorily absorbed from the G.I. tract, their action starting in $\frac{1}{2}$ hr. and lasting for 6-8 hours. They are widely distributed in the body and excreted in urine and milk. Their fate in the body is not known.

(b) These drugs produce their antithyroid action after a latent period, during which, stored thyroxine continues to act and when this is depleted, the action of thiourea compound starts. There is a marked subjective improvement, diminished sweating and tremor, drop in pulse rate, BMR and gain in weight.

(c) Some of the compounds inhibit the action of thyroid hormones peripherally, in the tissues and not only block the calorogenic response but the effectiveness of thyroxine in suppressing thyrotropine, is also reduced. The rate of diiodination of thyroxine is also minimised by some. It thus appears that they interfere with the binding of the hormone, both at the site of action, as well as, their degradation.

(d) The hormone synthesis is interfered with, in the glands, mainly by inhibition of binding of iodine into the organic form by (i) completely inhibiting the oxidation of iodides by the peroxidase system or (ii) by depleting the source of H_2O_2 . (iii) by reduction of iodine as soon as formed or by (iv) the blocking of coupling of iodotyrosines to form iodothyronine.

Toxicity: (a) *Allergic reactions*: skin rashes, urticaria, drug fever.

(b) *Blood dyscrasias*: Leucopenia and agranulocytosis. If these occur, the therapy is to be stopped.

(c) *Other side effects*: Arthritis, oedema of extremities, lymphadenitis and jaundice.

Propyl thiouracil, iturmil and mercazole are relatively less toxic, compared to others, the relative incidences of side-effects, in a general

manner, being thiourea-16%, thiouracil-10%, methylthiouracil-13%. Propyl thiouracil-1.6%, mercazole-6%.

	<i>Mode of action</i>	<i>Nature of action</i>	<i>Course of treatment</i>	<i>Remissions%</i>	<i>Special indications</i>	<i>Side effects</i>
Lugol's iodine	Iodine supply and TSH block	Rapid, incomplete and temporary	Short therapy	90	Thyroid storm	Iodism
Propyl thiouracil	Inhibition of thyroxine formation	Slow but more complete	6-12 months	50	Inoperable cases	Agranulocytosis
Imidazoles	—do—	Potent and fast action	—do—	60	—do—	—do—
I^{131}	Tissue destruction	Slow but complete action	Often a single dose	80	Malignancy	Myxoedema

Iodine and Thioamides compared and Combined: This is often envisaged, due to different mechanisms of action of these 2 groups of antithyroid drugs. The *role of iodine* in hyperthyroid states, is to reduce hyperplasia, vascularity and facilitate *colloid storage*, thus normalising the gland, while that of *thiourea derivatives* is to depress the thyroid function and inhibit thyroxine synthesis. However the actions of the former are variable, while that of the latter, more predictable and consequently combination therapy is more often advisable.

That is why, in *thyroid surgery*, it is customary to *prepare* the patient with *iodine*, followed by *mercazole* for 2-3 weeks, followed by *iodine again*. After the discontinuation of *mercazole*, a partial thyroidectomy is carried out and thereafter, the *postoperative mercazole therapy*, is again given for a short while, with a view to achieve the best possible therapeutic benefit for the patients.

Medical Care of Thyrotoxicosis: In spite of all these, medical care still plays a vital role in the overall management of thyrotoxicosis. Besides the symptoms of hyperthyroidism, increased activity of the sympathetic system and the accelerated neuromuscular excitability, palpitation, insomnia, sweating and raised B.M.R. are all to be taken into consideration for the relief of the patient. Medical treatment has not only a vital role in the prevention, palliation and even cure of the patient but it is a necessary adjunct also for the smoother conduction, even of

surgery and better ulterior results. It reduces the relapse rate after subtotal thyroidectomy and is specially indicated in cases where there is too great a surgical risk, in diffuse goitre and in cases of refused operation. *Surgical treatment* is particularly indicated in cases of recurrences, even after best medical care and in nodular goitre with or without signs of thyrotoxicosis.

The following *lines of treatment* are generally advocated:

(a) Complete mental and physical rest, with phenobarbitone sedation.

(b) Adequate carbohydrate and protein intake, around 0.75-1 gm/kg, to meet with the exigencies of increased metabolism, with also a thiamine intake of about 5 mg/day.

(c) *Propyl thiouracil*—200-400 mg/day for 12 months; *Methyl thiouracil*—400 mg/day or *Ticpazole*: 20-30 mg/day or *Lugol's iodine*.

(d) I^{131} , in variable doses of 4 mc. or more, 1-3 doses I.V. as required, is specially indicated in (i) Hyperthyroidism of elderly persons and with inveterate cardiac conditions. (ii) Hyperthyroidism associated with nodular goitre. (iii) Threatening thyroid malignancy and (iv) Remissions not occurring in spite of prolonged antithyroid therapy, or in cases of relapses after subtotal thyroidectomy.

INSULIN AND OTHER ANTIDIABETIC DRUGS

This would encompass the study of the following:

- (a) Insulin—the pancreatic hormone.
- (b) Recently discovered—oral antidiabetics.

INSULIN

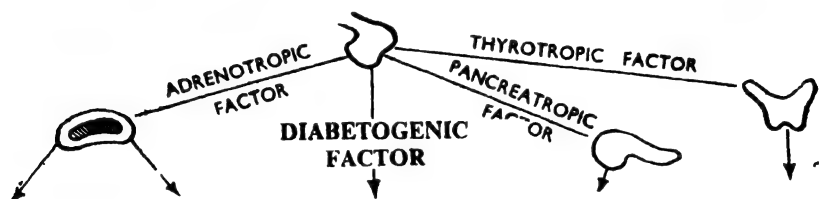
Historical: A great milestone in the annals of physiology and pharmacology, the knowledge of diabetes and insulin having progressively advanced during the last 75 years, through the following stages:

- (a) In 1889, Von Mehring and Minkowski produced and cured diabetes in dogs, by ablation and grafting of pancreas.
- (b) In 1922, Banting and Best isolated an active pancreatic extract and in 1926 (along with Abel) *crystalline insulin* was isolated.
- (c) In 1924, Houssay showed the role of the pituitary gland, in the causation of diabetes and in 1937, Young produced permanent diabetes in dogs with anterior pituitary extract.

- (d) Since then, ceaseless searches have been made for finding out a suitable dosage-form and an ideal preparation of insulin and from 1942, several *oral antidiabetics*, have also been discovered.

Carbohydrate Metabolism: Inspite of bafflingly advancing biochemistry, the mysteries of carbohydrate metabolism still remain fascinatingly intriguing and complex, with many missing links.

It is obvious that a large number of factors are implicated in this process viz. (a) Pancreas, (b) Pituitary (c) Adrenal cortex and medulla (d) Thyroid and (e) Liver.



Illus: XXX Endocrine control of carbohydrate metabolism.

Adrenaline	Corticosteroids	Hyperglycaemic factor	Insulin Liver	Thyroxine Tissue
Glycogenolysis and carbohydrate utilisation	Diabetogenic glyconeogenesis.	Increased formation and decreased utilisation of CH, resulting in hyperglycaemia	Increased glycogen formation	Increased sugar utilisation. & oxidation of carbohydrate.

The hypothesis that in the diabetes of *young people*, insulin mechanism is more at fault and in *diabetes gras* of elderly people, the pituitary factor is important, has not been borne out by substantial facts.

Insulin Antagonists: Not yet fully understood.

- Insulin favours the conservation of energy and storage of sugar, thus acting as an *anabolic hormone*.
- Vagal stimulation and adenoma of islets, provoke hyperinsulinaemia, whereas degenerative changes of the islets, produce opposite effects. Insulin secretion seems to be regulated by blood sugar level.
- Diabetogenic hormone, adrenaline, corticosteroids and thyroxine antagonise insulin action and act as *catabolic hormones*.
- Glucagon* or H.G.F., produced by the alpha cells of islets of Langerhans, under stimulation of *diabetogenic hormone*, also acts antagonistically to insulin. It induces hyperglycaemia by

accelerated glycogenolysis, in liver, like adrenaline. It does not antagonise insulin action in tissues, nor is it considered to be directly involved in the aetiology of diabetes, but it helps in the mobilization of glucose from muscles, thus providing a substrate for extra hepatic action also.

Chemistry of Insulin: It is a complex protein of polypeptide structure, having a molecular weight of 6000. It tends to form an aggregate of 2-6 molecules. It is composed of 52 amino acids of 17 different varieties, arranged in two different chains, having a disulphide linkage. The reduction of the disulphide linkage results in its loss of activity. It contains 0.3-0.6% of sulphur and on hydrolysis, like all other proteins, gives a number of amino acids—tyrosine, cystine, arginine, histidine, lysine, proline, glutamic acid, leucine, serine and phenyl alanine.

Preparation of Insulin: Insulin is prepared from mammalian pancreas, collected fresh and intact, as trypsin destroys it rapidly. It is then frozen, minced, treated with stronger alcohol and evaporated. The precipitate is dissolved in water and insulin separated out by isoelectric point precipitation. The powder is made into solution and if kept in cold storage at pH 3-4, it retains its potency for 18 months. It is, supplied in rubber capped bottles, containing 10, 20, 40, 50, 100 units/ml one insulin unit representing the hypoglycaemic activity, contained in 1/22 mg of standard international insulin powder. The appearance of any precipitate in the solution, indicates its deterioration.

Modes of Study: These are diverse and the assay methods have been indicated in Chapter—6.

- (a) Determination of 'hypoglycaemia effect' in normal rabbits.
- (b) Convulsion method in normal rats and mice, indicating the degree of hypoglycaemia, and above all,
- (c) Study of hypoglycaemic effects in rabbits and rats after induction of experimental *alloxan diabetes*.

Alloxan or *mesoxal urea*, is chemically related to uric acid. In a dose of 40 mg/kg, it produces hyperglycaemia in 1-4 days, which becomes steady within a week. The antidiabetic drugs are then screened in those animals by blood sugar estimation, according to *Folin Wu* or *Hagedorn-Jensen methods* and compared to a known drug. It is better indicative of hypoglycaemic effect than on the normal blood sugar level.

Types and Dosage-Forms: These are innumerable, as diabetes is a life long metabolic disease and insulin has to be used parenterally.

The action of crystalline insulin being of short duration, efforts have been made for discovering suitable preparations with prolongation of action, and simpler modes of administration. Insulin is available in three different forms, at present.

I. Crystalline or Plain Insulin: Available as clear solution containing 20, 40, 80, 100 units/ml.

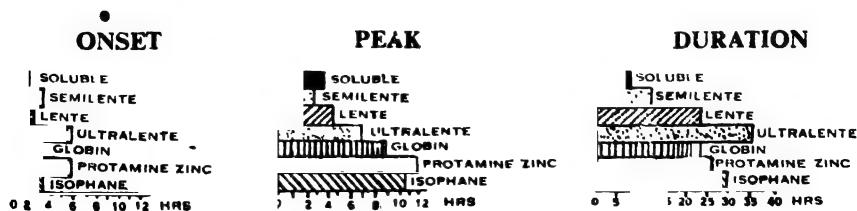
II. Retard or Modified Insulin: Prepared either by a loose combination of crystalline insulin with metals, fish sperm or other proteins or by modification of *isocyanide linkage* in insulin molecule, giving *iso-* and *di-insulins*, the purpose of modification being the release and supply of insulin slowly, from the combinations, for prolongation of action.

The important preparations are: (i) P.Z.I. (Protamine-Zinc Insulin), (ii) Histone-Zinc-insulin, (iii) Globin-insulin (iv) Isophane or N.P.H. Insulin, (v) Polyvinyl (Subtosan insulin), (vi) Iso- and di-insulin. They usually have a pH of 7.2 and PZI, 0.2 mg of Zn/100 units of insulin, mutually miscible. It is customary to have a 3:1 (crystalline: retard insulin) combination, for immediate and prolonged actions. *Subtosan insulin* is very viscous and *di-insulin* has the longest action of 72 hours.

III. Lente Insulin: These are slowly acting insulins, like the above—‘old friends in new garbs’, as expressed by some workers. There are three principal types:

1. *Semilente*: This is amorphous and has a duration of action of 12-16 hours.
2. *Lente*: A mixture of *ultra* and *semilente*, in a ratio of 7:3, with duration of action for 24 hours.
3. *Ultra lente*: Having insulin crystals of larger size and duration of action for 30 hours.

Action: Insulin action is primarily related to its hypoglycaemic effect. The manner in which, the different preparations influence the time of onset, duration and peak effect on blood sugar level, is graphically shown in *Illus. XXXI* and underlying *comparative table*.



Illus. XXXI—Comparative action of Insulin preparations

	<i>Crystalline Insulin</i>	<i>Globin Insulin</i>	<i>Isophane Insulin</i>	<i>Lante Insulin</i>	<i>P—Z Insulin</i>
Onset	1 hour	2-4 hrs	1-2 hrs.	1-2 hrs.	4-8 hrs.
Peak effect	2-3 hrs.	8-16 hrs.	10-20 hrs.	12-20 hrs.	16-24 hrs.
Duration	6-8 hrs.	16-24 hrs.	24-32 hrs.	24-28 hrs.	30-48 hrs.

There are several factors which modify insulin action. Some of these are:

- Solubility*: This is related to absorption and prompt action of a given preparation. Insoluble colloidal preparations produce slower action.
- Route of administration*: This also should determine the rapidity of action but as insulin is mostly used S.C. only, this has hardly any bearing.
- Repeated injections* in the same area retard its absorption, particularly in cases of retard insulin.
- Muscular exercise* diminishes insulin requirement, due to the greater utilization of glucose.
- In infection, acidosis and anaesthesia*, due to the reduced sensitivity of the patient, larger doses of insulin are needed for producing the same effect.

Metabolism: This is still somewhat controversial: (a) *As a protein, Insulin is very little absorbed* from the G.I. tract and consequently, there is no justification in using insulin antidiabetic pills, orally. The route of choice is S.C. and I.V. route is seldom used, even in a diabetic coma. Insulin is rapidly destroyed in the body and only a small quantity excreted in urine. Impure insulin is destroyed more slowly but may give local and allergic reactions. Unlike *endogenous insulin* which is secreted according to blood sugar needs, *exogenous insulin* produces a fluctuating concentration and action on blood sugar level.

(b) In *growth-onset* diabetes, *secretion* of insulin is impaired and in *maturity-onset* form, its secretion is normal or even greater.

(c) There is increased rate of *destruction* of insulin in cases of diabetes and there may be decreased sensitivity of target cell of diabetics and also formation of *anti* substances or *insulin antagonists*—insulinase

and reduced glutathion, splitting the disulphide linkage and amino acids.

(d) Insulin is transported, bound with antibodies or basic proteins of special types and deposited in fats. Study with *labelled insulin* has not confirmed this hypothesis and assay of plasma insulin is also somewhat difficult. Half of the hormone is destroyed in its passage through the liver, where, it is metabolised and no significant quantity of biologically active insulin is excreted in urine. The degradation of insulin by *insulinase* has been postulated but its level does not always corroborate the clinical problems.

Insulin Resistance: Endogenous secretion hardly exceeds 30 units per day. Clinically, patients requiring more than 200 units/day, are taken as *insulin resistant*, which are of two types:

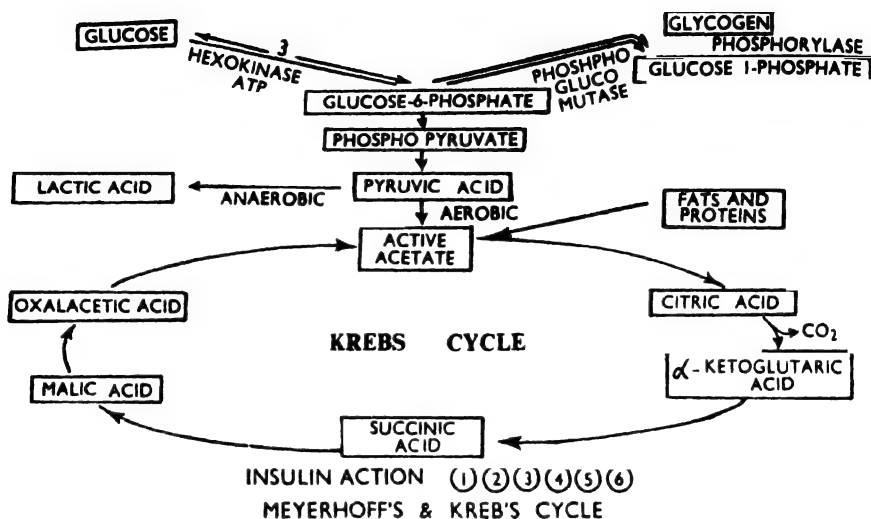
- (a) *Acute*: after surgical trauma, emotional disturbances, infections, ketoacidosis, lipaemia and hypercorticism.
- (b) *Chronic*: from high plasma binding antibodies, endocrine disturbances and lipotropic diabetes, with absence of normal fat deposits, hyperlipaemia and corticisms. For this, change of brand of insulin and use of oral antidiabetics are recommended. In cases of insulin resistance, presence of *synalbumin*, a *globulin*, has been detected in plasma, as *insulin antagonist*, acting on the disulphide linkage.

Untoward Effects: Besides insulin over-dosage hypoglycaemia, discussed later, the principal untoward effects are:

- (a) *Lipodystrophy*: at the sites of the injection, and more so with retard insulin.
- (b) *Insulin presbyopia*, occurring from the change of sugar level after treatment, which affects the lens, temporarily. It usually corrects itself after a few weeks of cessation of therapy or by changing the lens.

Steps of Action: For understanding the rationale of insulin action, it is necessary to review the complicated role of this important hormone on the *normal*, as well as, *abnormal* carbohydrate metabolism, as in diabetes mellitus. This role obviously involves the *enzymatic*, as well as, *hormonal* interplay, at the cellular level of metabolism, of carbohydrate, fat and protein, in all their ramifications.

For this, it is necessary to take *normal glycogen*, as well as, *Kreb's Cycles*, in this mechanism for consideration, as detailed below:



Illus: XXXII: Carbohydrate metabolism and sites of action of Insulin

Insulin, as seen above, acts on the following *six steps* of carbohydrate metabolism:

- Steps 1 & 2 :** Facilitation of entry of glucose into cells and conversion to glucose—1-phosphates of glycogen by the process of phosphorylation.
- Step 3 :** Facilitation of conversion of glucose to glucose—6-phosphate by *hexokinase reaction*, in the presence of A.T.P.
- Step 4 :** Increased phosphopyruvate conversion to pyruvic acid and subsequently, to active acetate.
- Steps 5 & 6 :** Incorporation of active acetate into fatty acids and proteins and their final disposal in the form of CO₂ with simultaneous synthesis of high energy phosphate bonds of ADP and ATP.

The above facilitate the (a) Conversion of glucose and its storage as glycogen. (b) Prevention of gluconeogenesis and (c) Prevention of formation of ketone bodies, because of complete oxidation of the fat.

The biochemical changes strongly suggest that the varied actions of insulin are in fact, dependent on the single fundamental principle of an interplay of a regulating action in the synthesis of high energy phosphates ADP—ATP, at enzyme level, resulting in their critical increase, facilitating carbohydrate metabolism appropriately.

Physio-Pathology of Diabetes: (a) In this disorder, sugar metabolism is grossly disturbed, liver and muscle sugars are depleted and most of these are poured into circulation and urine, resulting in *hyperglycaemia* and *glycosuria*.

- (b) After forced labour, the muscles are further depleted of sugar and not refilled and this results in an imperfect utilisation of glucose, as a source of energy.
- (c) As a result thereof, the normal ratio of CH. of 2:1, is disturbed, leading to an improper combustion of fat and consequent formation of *beta hydroxy butyric acid*, *aceto acetic acid*, *acetone* and *ketosis*. At this juncture, there is breakdown of proteins, also, for the formation of sugar (*neoglucogenesis*), involving the process of transamination. *Blood and urine nitrogens* are increased.
- (d) The critical role of insulin in rectifying the above derangements, is its unique ability for conservation, storage, transport and utilization of glucose, as observed in *Kreb's cycle*. Decrease of gluconeogenesis, glycogenolysis and lipolysis after insulin, are also important factors related to the hypoglycaemic action.
- (e) As a result of this, blood sugar is mobilised to tissues, oxidised and fats are properly burnt. Blood sugar level comes down to the normal level of 80 to 120 mg%, glycosuria and ketosis disappear and liver is refilled with glycogen. There is thus a veritable return to normality, almost a resurrection of the patient, by these physio-biochemical mechanisms, 'constituting' the rationale of use of insulin in diabetes mellitus', which implies the knowledge of—(a) disease (b) drug and (c) scientific basis of •use of insulin, as a 'specific', in the therapy of diabetes.

Insulin Hypoglycaemia: If however, by chance, an overdose of ordinary or Z.P. insulin is given, the patient gets flushes, fainting, sweating, tremors, delirium and coma. In cases of Z.P. insulin, this becomes a dangerous affair as its effect is of a prolonged nature and much more difficult to control. When the blood sugar level falls below 70 mg%, it is known as *Insulin hypoglycaemia*. This should not be confounded

with *diabetic coma*, the distinguishing features from *insulin coma*, being, as given below:

Signs	Diabetic Coma	Insulin Coma
Skin	Dry and flushed	Moist
Tissues	Dehydrated	Normal
Blood Sugar	High	Low
Glycosuria	Present	Absent
Acidosis	Present	Absent
Breath	Acetone smell	Not so

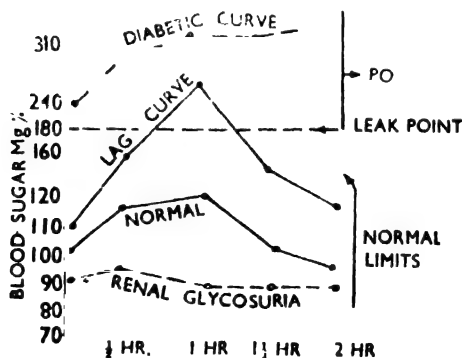
Treatment of (i) *Insulin hypoglycaemic coma* comprises immediate uses of: (i) I.V. Glucose saline, (ii) Liq. adrenaline HCl S.C. and (iii) Withholding of insulin and that of (b) *Diabetic Coma*: (i) Large doses of insulin and (ii) Glucose I.V., and (iii) Sodium bicarbonate.

Insulin Therapy: Major indication of insulin therapy is only one and that is in *Diabetes Mellitus*.

Minor indications are many, as in—(a) Anorexia nervosum, (b) Cyclic vomiting and (c) Underweight conditions, for which small doses are preferred, (d) Schizophrenia: insulin is preferred to cardiazol but not E.C.T. therapy (e) Acute alcoholism: glucose, insulin and thiamine are prescribed.

Management of Diabetes Mellitus: This comprises (a) Correction and regulation of diet, (b) Drug therapy and (c) Management of complications.

Pre-requisites: (a) Examination of urine for sugar and ketone bodies. (b) Blood sugar and glucose tolerance tests. The different types of *blood sugar* curves, normal, potential, renal and diabetic, are as shown below:



Illus: XXXIII. Normal and abnormal Blood Sugar Curves

When diagnosis is established, type and severity of the disease are to be considered. In *mild cases*, control of diet on the principle of 2000 calories with CH, protein and fat, in a ratio of antiketogenic: ketogenic—1 : 1.6, which would roughly amount to CH—100 gms. protein—100 gm and fats for the rest, with a distribution of caloric requirements as 1/5 in breakfast and 2/5 each, for lunch and dinner. *Lawrence's diet sheet*, categorising food stuffs, according to their percentage composition of food ingredients, may be consulted for working out the definite *diet schedule* for diabetics. In *obese diabetics*, there is need for reduction of weight.

In spite of regulation of diets, if the urine is not sugar-free, or in cases of fairly *severe* diabetes of young people, *insulin therapy* should immediately be resorted to, without any undue restriction of carbohydrates. From the studies of the *Mulangracht school of workers*, it is now apparent that *with insulin therapy*, adequate amount of CH, ensures better appetite, increased sensitivity to insulin and even increased secretion of endogenous insulin.

Details of Therapy: Insulin is one of the few drugs, which does not follow any strict *dosage schedule*. Though the official dose range is 5-100 units, it has to be worked out in every case, on the basis of 1 unit of Insulin metabolising 1.5-2 gm. of *excess sugar*, i.e. the quantity of sugar, excreted in 24 hrs, urine.

(a) To start with, *crystalline insulin*, in morning and evening doses: $\frac{1}{2}$ hr. before meals, the morning dose being slightly bigger than the evening one, should be used and the doses gradually increased till urine becomes sugar free.

(b) After the patient has stabilised to an appropriate dose of crystalline insulin, as judged from his urine and blood sugar levels, a combination of *ordinary* and *retard insulin*, in a proportion of 2 or 3:1 or some of the special insulins, may be used.

(c) While using insulin, hypersensitivity, as well as, *insulin resistance* of certain patients, should also be borne in mind and the therapy accordingly adjusted.

Treatment of Diabetic Coma: This is an emergency condition, in which, CH metabolism has been reduced to the minimum and there are associated toxic manifestations from dehydration, salt depletion, vomiting and circulatory collapse, all of which demanding active therapeutic measures with (i) 100-200 units of crystalline insulin and (ii) 500 gm.

of glucose with coramine, during the *first day* and (iii) half of it, during the 2nd day of the therapy.

Glucose Uptake by diabetic liver and more so in coma, is usually slow, and fructose, which is more readily metabolised, may be used. After full control of coma, the usual antidiabetic treatment is to follow.

Patients under insulin therapy should be asked to carry sugar with them and use *sacharine* or *dulcin*, as sweetening agents, instead of sugar.

ORAL HYPOGLYCAEMIC AGENTS

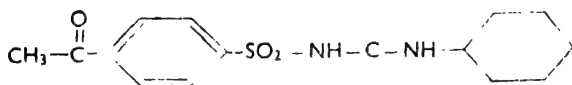
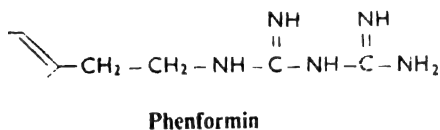
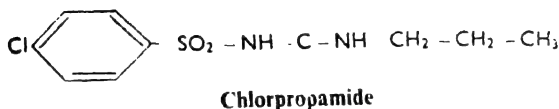
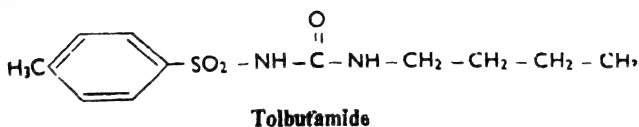
The limitations of Insulin therapy in its mode of administration and use, induced many workers to explore other dosage-forms of drugs capable of producing hypoglycaemic effect in diabetes. It was observed that *salicylates*, the plant product, *synthalin*, and some of the *guanidine* derivatives also possessed this action but could not be used because of toxicity. It was further observed that diabetic pills and other vegetable drugs were of dubious value, in this respect. Of late, the work of Jambon (1942), Bovet and Dubost (1944) and others, revealed hypoglycaemic effects of *sulphonylurea* and *biguanidine* compounds, in experimental studies. This was the starting point for the introduction of oral antidiabetics, which now comprise two principal chemical groups of (a) *Sulphonylurea* and (b) *Biguanidine* derivatives.

Some of the important members and their chemical structures are given hereafter:

Chemical type	Generic name	Proprietary name	Tablet size mg.	Daily dose in gm	Half life in hrs.	Duration of action in hrs.
<i>Sulphonylurea</i>	Tolbutamide	Rastinon, Orinase		500	0.5-3.0	4-6
	Acetohexamide	Dymelor		250,500	0.25-1.25	6-8
	Chlorpropamide	Diabenese	1/i.e. 100-250		0.1-0.5	30-36
	Tolazamide	Tolinase	1/i.e. 100-250		0.1-0.5	7
	Carbutamide	Nadisan	500		0.5-3.0	20
	Tolcyclamide	Diaboral	200		0.2-1.2	—
<i>Biguanide</i>	Phenformin HCl.	DBI	25		0.05-0.2	3
	Phenformin HCl. Timed release	DBI-TD	50		0.5-0.2	3
	Baformin	Silubin, DBV	50-100		0.05-0.3	4-6
	Metformin	Diabex	500		0.5-1.0	8-10
						12-18

Of these, *carbutamide*, on preliminary clinical trial, was found to be *toxic* and withdrawn from market. Amongst the others, *tolbutamide* is more frequently used, though *Chlorpropamide* and DBI are the most potent.

Chemistry: The chemical structure of important oral antidiabetics are shown below:



Illus: XXXIV. Structure of Oral Antidiabetics

All the effective compounds are arylsulphonylureas with substitution in benzene and urea groups. In tolbutamide, the aryl group is tolyl and urea substitution is by butyl. There is an amino group in the benzene ring in antibacterial sulphonamides. Its substitution by a methyl group, as in tolbutamide, removes this activity. In chloropamide, chlorine is at para-position to benzene and urea substitution is by propyl.

SULPHONYLUREAS

Metabolism: All the compounds are promptly and completely absorbed from the G.I.T. They are distributed in E.C.F. and plasma, where they are partially bound to serum protein. Their rate and means of degradation, however, vary with different compounds.

Carbutamide BZ 55 (Nadisan) is one of the earliest in the series. It is acetylated in the liver and completely excreted in urine, in about 36 h. However, as stated above, being toxic, it is seldom used and has been withdrawn from market.

Tolbutamide (Orinase, Rastinon), is one of the compounds in general use. It is converted to carboxy-derivative, in the liver and is quickly excreted by kidneys. Its half-life is of a few hours in the body. Its hypoglycaemic effect lasts for 6-12 h. It can cause teratogenic effect.

Acetohexamide: It is metabolised to 1-hydroxy hexamide, which is much more potent than the precursor. Though its $1/2$ life in circulation is for $1/2$ -2 h., that in the body, is for 4-5 h. and a time-course, slower than tolbutamide. It is also excreted in bile and stool, besides urine. *Tolazoline* is much more slowly absorbed and excreted and has a longer duration of action of 10-14h. *Chlorpropamide* is one of the longest acting compounds, remaining in blood for 36 h and in the body several days. For these long acting compounds, renal and hepatic clearance condition is to be kept in view, to avoid toxicity hazards.

Glymidine: a suitable pyrimidine derivative, which is not sulphonylurea exactly, but is closely related to it in metabolism and action and has no antibacterial property. Its half-life is 4 h and it is fairly well tolerated. It may be used in patients who do not tolerate other compounds well and are sensitive to them.

Mode of Action: (a) This is not fully settled, as yet. Despite the earlier controversies, the rôle of pancreas in the hypoglycaemic effect of sulphonylureas, is essential, inasmuch as, their action is related to the degree of granulation in the islet cells, which are extensively damaged in juvenile diabetes and less so in the maturity-onset type of obese, elderly persons. (b) After administration of sulphonylureas, insulin is released from the pancreas. Its level increases in plasma but decreases in pancreas. Normally, they do not act in pancreatectomised animals, but with higher doses, they may do so, by some direct action, on the liver. (c) The other hypotheses are (i) Inhibition of glucagon and stimulation of insulin production (ii) Decreased glucose output from liver and inhibition of phosphorylase synthesis, (iii) Increased glucose uptake by muscles and inhibition of insulin destruction by insulinase.

Adverse Reactions: In about 6% of cases. They are similar in nature but the frequency varies. The long acting group is the worst in this respect:

- (a) Increased gastric secretion, heartburn, nausea, abdominal cramps and diarrhoea.

- (b) Confusion and ataxia from chlorpropamide.
- (c) Increased flushing reaction after alcohol, as with disulphuram, after carbutamide and chlorpropamide.
- (d) Hypothyroidism, granulocytopenia, cholestatic jaundice, preceded by fever, skin eruption and photosensitivity.

They occur after 2-3 months of high doses of chlorpropamide.

Advantages: Their advantages over insulin are:

- (a) Comparative ease of administration.
- (b) Endogenous release of insulin resembling more the normal secretion, the physiological phenomenon.
- (c) They pass through liver and produce effects on liver glucose first, this is unlike injected insulin which floods the peripheral tissues before it reaches the liver.
- (d) Less allergic reactions. Patients allergic to exogenous insulin or having antibodies against it, can be managed better with sulphonylureas.

Dose: *Tolbutamide*—500 mg. tablet, 3 gm. or 6 tabs initially and 2 tabs. as maintenance dose/day. *Chlorpropamide*—100 and 200 mg/tabs. 500 mg. initially and 100 mg. maintenance dose/day.

Uses: 1. *Diabetes mellitus*. Maturity-onset type, in which, pancreas is functioning and the patient does not need more than 25-30 units of insulin for control of hyperglycaemia. They act better in middle-aged, obese patients, along with diet regulation and reduction of weight. In cases of infection or any other complication, parenteral insulin must be given.

The failure of therapy may be due to change in the metabolism of the individual drug and consequently, the patient should be switched on to another preparation. If a patient cannot be maintained with 0.5 mg of chlorpropamide, 2 gm. of tolbutamide, 1.25 mg. of acetohexamide or 0.75 mg. of tolazamide daily, larger doses should not be tried. Their effects are additive with insulin and phenformin and they may therefore be used in combination, for better management of some cases. Their effectiveness varies also with time—from weeks to 6-12 months of treatment. Therefore, careful surveillance is needed for averting complications. Their effectiveness is enhanced by other drugs—phenylbutazone, phenylamidol, bis-hydroxy coumarin and sulphaphenazole, salicylate, proteresis and MAOI.

2. *Diagnostic Tests:* (i) Tolbutamide in insulinoma—markedly reducing blood sugar level in a dose of 1 gm. given I.V. in 2 mins. (ii) Useful also in testing borderline patients for suitability in glucose tolerance test.

3. *Diabetes Insipidus:* Chlorpropamide is sometimes used in this condition and its action is similar to that of vasopressin. The antidiuretic action is from reduction of free water clearance without affecting glomerular filtration or osmotic clearance. Other compounds do not claim these effects. *Dose:* 0.25-0.5 gm/day or more. It may act by enhancing the effects of low concentration of vasopressin, in the kidney.

BIGUANIDE DERIVATIVES

They represent 2 molecules of guanidine after elimination of one molecule of NHA. There are several of them, possessing hypoglycaemic properties, but only one is used in therapeutics.

Phenformin—or phenylethyl biguanide (DBI), is a white crystalline powder, marketed as *tablets* of 25 mg. and time-disintegration *capsules* of 50 mg each. It is absorbed from the G.I. tract and its duration of action is from 6-14 hours.

Mode of Action: Unlike sulphonylurea derivatives, the biguanides show little effect on the normal blood sugar level. Phenformin, however, potentiates the action of insulin, *in vivo* or *in vitro* experiments and may act by antagonising the anti-insulin factors. It also decreases glucose absorption from the intestine.

Phenformin acts differently from orinase or diabenese. It enhances anaerobic glycolysis and glucose utilisation. However, effective doses do not increase blood lactic acid level. It is believed to cause weight-loss in obese patients, though not always. It has been suggested that insulin destruction or depression of insulin antagonists, is provoked by it, accounting for its antidiabetic action.

Toxicity: The average dose is 1 mg/lb of body weight. Any overdose may cause anorexia, vomiting, abdominal cramp and a peculiar metallic taste in the mouth. In some cases, though rare, 'lactic acidosis' has also occurred in hepatic, cardiac and renal cases, in advanced stages of toxicity.

Use: The same as for sulphonylureas: maturity—onset, mild diabetes. *Tablets* of 25 mg/2 tabs/day, increased to 100 mg/day. It is often used in combination with any of the members of the other group and also

in resistant cases of sulphonylurea and insulin, after prolonged therapy. The combination of oral antidiabetics and also insulin is justified because of their different mechanisms of action. The therapy has been observed to be beneficial, in 70% of properly selected cases. Combined therapy with insulin, in the growth-onset type, though controversial, is sometimes used for stabilisation of unstable sugar levels, by this treatment.

ACTIONS ANALYSED

Major Action	Insulin	Sulphonylurea	Phenethylbiguanide
	Glucose trans- ference to cells	Degree of insulin secretion	State of anaeroba- sis
Insulin secretion	Decreased	Increased	Decreased
Glucose uptake-peripheral	Increased	Increased	Increased
Gluconeogenesis	Decreased	Decreased	Decreased
Liver glycogen	Increased	Increased	Decreased
Blood sugar lowering	Marked	Moderate	None
Marked hypoglycaemia	Common	Rare	None
Lactate utilisation	Increased	Increased	Decreased

So far as relative merit of the important compounds studied, it is difficult to assess correctly. The choice in use, is to try *chlorpropamide* with longer duration of action if *tolbutamide* fails and when *chlorpropamide* fails, *phenformin* may be tried. None of them however, act as a real substitute for insulin and also in diabetic coma. As stated earlier, they are to be tried in *mild cases* only, with blood sugar controllable with 25-30 units of insulin, but not to insist on their continued use, if ineffective after a short trial. They may be combined with insulin in certain cases, in which, they may act as useful adjuvants.

The oral antidiabetics, which have been extensively used now, have posed another problem of importance in the form of *drug interaction*, particularly in the clinical uses of *tolbutamide*, which is strongly bound in plasma proteins where, it can displace bis-hydroxy coumarine, thus leading to an increased anticoagulant action. This however has not been accepted by others. Probably, the order of administration is important. The thiazide diuretics oppose the actions of sulphonylureas.

In spite of this, the oral antidiabetics have opened a new line, in the treatment of diabetics. Despite their present shortcomings, it is likely that better drugs will be discovered in future, obviating the present

difficulties of replacement therapy with insulin, viz. parenteral administration, one or two injections per day and almost lifelong therapy, in many cases. As it often happens, in many cases, after years of treatment, it becomes a problem to find any suitable site for S.C. injection, each preceding one, leaving some induration and fibrosis, at the site of its injection.

CHAPTER

54

PHARMACOLOGY OF STEROID HORMONES

CORTICAL, TESTICULAR AND OVARIAN HORMONES. NATURAL ACTIONS AND USES

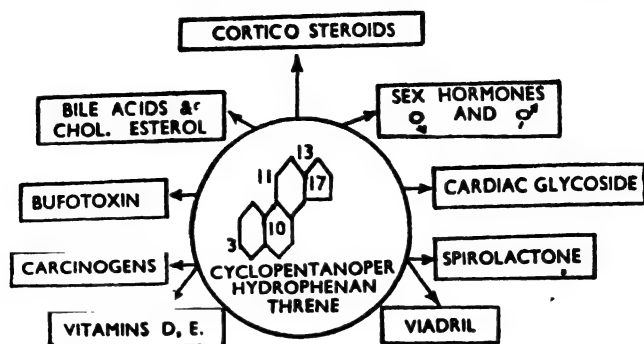
[The cyclopentano-perhydro-phenanthrene ring, like phenothiazine, quinoline, indole and several others, constitutes major landmarks in chemical pharmacology and pharmacotherapeutics. The first is the basic nucleus for cholesterol, digitalis glycosides, vitamin D, corticosteroids and sex hormones, constituting the special branch of *steroid chemistry*, with promising therapeutic possibilities.

The *cortical hormones* comprise *gluco-* and *mineralo-corticoids*, as well as, *sex-hormones*. They are elaborated under the influence of ACTH. Cortisone, hydrocortisone, prednisone and prednisolone are *glucocorticoids* with predominant anti-inflammatory, antiallergic and proimmunizing action and used for collagen diseases, asthma, other allergic disorders, gout, leukaemia, skin and joint troubles, nephrosis and infective hepatitis. DOCA, 9- α -hydrocortisone and aldosterone are predominantly *mineralocorticoids* and used in correcting the mineral metabolism, as in Addison's disease. On prolonged use, they may produce hypopituitarism and hypercorticism.

The *male sex hormones*—testosterone propionate and methyl testosterone, find their uses in: (a) hypogonadism (b) as oestrogen antagonist, in uterine bleeding and breast cancer and in (c) cryptorchidism.

Of the *female sex hormones*, follicular and corpus luteal, the *oestrogens* may be natural, semisynthetic and synthetic esters or conjugates. They are oestrone, progynon, stilboestrol, diethylstilbestrol, mestibol, TACE and ethinyl oestradiol. They are used in: (a) hypogonadism (b) menopausal disorders (c) enlarged prostate and (d) senile vaginitis. *Progesterone*, hydroxy-progesterone and lutealins are used in: (a) threatened abortion (b) metrorrhagia haemorrhagica and (c) hyperemesis gravidarum. Often the two groups are combined in a therapy, with the idea that, physiologically also, they act interdependently. Further, *progesterone-oestrogen mixtures*, in different forms and concentrations, also find their uses as *oral contraceptives* and antifertility agents, detailed separately in Chapter 55.]

'Steroid chemistry' constitutes remarkable advances in modern medicine and a large number of therapeutic agents have been obtained from this single source, in recent years.



Illus: XXXV. Scope of Steroids at a glance

In the present chapter, it is proposed to study the following: (a) Cortical and (b) Male and female sex hormones.

Physiological Background: The adrenals are dual glands, comprising (a) Cortex and (b) Medulla, elaborating 'corticoids' and adrenaline, respectively. Besides their manifold physiological actions, both of them are concerned with meeting the needs of exigencies of day-to-day life, on long and short term basis. In addition to their intricate biochemical and metabolic roles, the cortex is also concerned with the synthesis of vitamin C. (c) The corticoids are indispensable for maintenance of life, while adrenaline with all its important actions, is not.

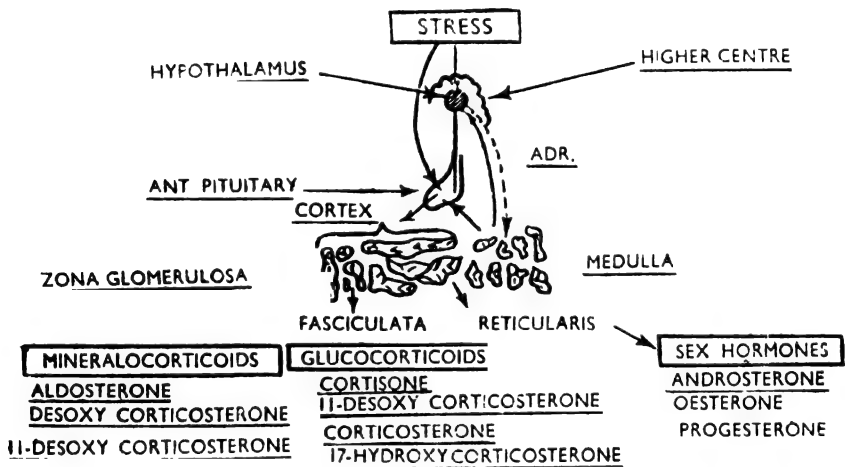
Historical: The cortex offers a fascinating example of growth of scientific knowledge during the past one century.

- (a) The memorable work of Thomas Addison (1855) on 'Addison's disease', which was a land-mark in the history of endocrinology. The systematic work of Brown-Sequard (1856) on endocrine deficiency syndromes by the ablation techniques, further established its role on scientific basis.
- (b) The preparation and study of the role of 'cortical extracts' by Swingle and Hartman (1930) and isolation and synthesis of nearly 30 crystalline steroids by the Kendall group of workers, during the past decades, further advanced this knowledge.
- (c) The relationship between the pituitary and the adrenal gland, established by Evan, Houssay and Collip (1926-1933) and the discovery of ACTH by Lee and Seyers, in 1943, were important links in the understanding of integrated hormonal activities in the body.

(d) The concept of *adaptation syndrome*, involving hypothalamus, hypophysis and the adrenal axis, by the Selye group of workers and knowledge of the therapeutic role of ACTH and cortisone and other steroids established by Hench, Reichstein and others by 1949, proved to be a final step in the advancement of our present knowledge in this complex subject.

These investigations have revolutionised medical thoughts in recent decades and though it is not possible to predict their future scope, fully as yet, the contributions have brought *Nobel Prize* to several of the workers—Hench, Kendall and Reichstein, indicating the intrinsic value of the problem and contributions therein made, opening newer vistas, for further work in the future.

Regulation of Secretion: This occurs through a series of complex mechanisms involving a chain of endocrines, represented diagrammatically below:



*Illus: XXXVI: Endocrine regulation of secretion and nature of corticosteroids**

Physiological Chemistry: Any stress or increased secretion of adrenaline results in the stimulation of hypothalamus, leading to ACTH and finally, corticosteroid secretion. The latter comprises:

- (a) *Mineralocorticoids*, secreted by *zona glomerulosa*.
- (b) *Glucocorticoids* from *zona fasciculata*.
- (c) *Sex hormones* from *zona reticularis*, all having the basic structure of 'cyclopentanoperhydrophenanthrene nucleus', as shown above.

In this *basic nucleus*, there are several strategic positions: 3, 10, 11, 12 & 17.

- (i) O_2 at C_{11} position, gives *cortisone*, while its absence, gives *desoxy-corticosterone acetate* or DOCA.
- (ii) In *aldosterone*, there must be a CO at position C_{17} .
- (iii) In *oestrone*, CH_3 is at position C_{13} , while in *testosterone*, there is an additional CH_3 at position C_{10} .

There are thus subtle differences in positions and radicals, which determine the type of a particular hormone. This leads to easier biotransformation, as well as, overlapping of actions sometimes.

General Adaptation Syndrome: The regulation of hormonal secretion has led to the concept of *general adaptation syndrome*, propounded by the Selye group of workers, in the causation of a number of diseases, designated as (a) *Collagen diseases*: rheumatoid arthritis and erythema nodosum, (b) *Hypertension* and nephrosclerosis, (c) *Allergic diseases*, (d) Infectious conditions, (e) *Psychosomatic* diseases and (f) G.I. disorders.

The underlying concept in the pathogenesis of all these diverse conditions, is that they all constitute a stress phenomenon with consequent changes in the functioning of the 'adrenohypophyseal axis', homeostasis, hormonal secretions and also tissue changes.

Cortical Syndromes: There are two major ones:

Addison's disease—This is a *hypoactivity* state, characterised by classical symptoms of (a) hypotension, (b) bronzing of skin, (c) adynamia, (d) maladjustment to thermal changes, (e) disturbances in fluid and ionic balances in the body and consequent (f) renal and circulatory failures.

Cushing's syndrome: It is on the contrary, a *hyperactivity* state, involving both pituitary and suprarenal cortex, associated with (a) sexual disturbances (b) hirsutism and (c) masculinisation of females.

CORTICOSTEROIDS

Of the different types of corticosteroids, referred above, the *gluco* and *mineralocorticoids* are mostly used in therapeutics.

Cortical Extracts: Both aqueous and oily, 1 ml representing 5 mg of hydrocortisone effects, are used. In adrenal crisis, 30-50ml. I.V. followed by 10 ml. and then 2 ml. I.M./2 hr, for 12 hours. In spite of isolated hormones, usefulness of the extract, cannot be ruled out.

Desoxycorticosterone Acetate: It was synthesised before its isolation, as it is present in the gland, in minute quantities. It is probably an intermediate compound during the synthesis of corticosterone and other hormones in the gland. The recent discovery of *aldosterone*, the most potent, salt retaining hormone, was foreshadowed because of this. It is a mineralocorticoid concerned with the retention of NaCl and excretion of K in the urine.

Aldosterone: A brilliant discovery representing the confluence of different lines of investigations, including chromatography. An extremely potent mineralocorticoid, its secretion is not influenced by tropic hormones but probably by extracellular fluid level. It was isolated from the adrenal blood and is closely similar to cortisone, chemically. Whether excessive aldosterone output is related to the oedema, is not established.

Cortisone: It was initially partially synthesised from desoxycholic acid but now complete synthesis has been achieved. It affects carbohydrate, fat, protein, purine and water metabolisms and also tissue enzymes, blood coagulation, gastric secretion, C.N.S. Immune-reaction and anti-inflammatory effects have been separately dealt with.

Hydrocortisone: It is probably the principal hormonal product of the adrenal cortex. Its effects are more similar to those of cortisone than others. It is more potent than cortisone in physiologic and antirheumatic action and is also possessed of local activity. It produces less central stimulation, is more soluble in body fluids and can be given orally also.

Prednisone and Prednisolone: Obtained from cortisone and hydrocortisone, they are 3-5 times more potent than their parent substances. Salt and water retention is minimum in their small therapeutic doses. Methyl prednisolone is 3 times more potent than prednisolone, on glycogen deposition and twice as effective in antiinflammatory action. It is used in 4 mg. doses.

Halogenated Corticoids: They have been prepared from the inactive prednisone and are extremely potent anti-inflammatory agents. 9-1 fluorohydrocortisone is used in a dose of 0.25-0.5 mg./day. It is also used as skin ointments.

Dosage Forms: *Cortisone:* (a) Tablet of 25 mg. each, (b) Injection of 5 and 25 mg/ml.

Hydrocortisone: (a) Tablet of 20 mg. (b) Sol. 5 mg/ml. (c) Ointment: 0.5-2.5%. Eyedrop 1%.

Doca: (a) 2-5 mg. I.M. (b) Pellet of 100-200 mg.

Prednisone and Prednisolone: (a) Tablets of 1, 2.5 and 5 mgs. (b) Injection: 2.5 mg/ml.

9-alpha-fluoro-hydrocortisone: (a) Tablet of 0.25-0.5 mg. (b) Ointment or lotion: 0.25%.

Aldosterone: 100-250/ μ g/day.

Triamcinolone, betamethasone, dexamethasone are also potent anti-inflammatory agents and suitable for oral administration.

Spirolactone: This is also a steroid which chemically resembles aldosterone and is marketed under the name of *aldactone*. When given orally, in a dose of 100-400 mg/day, it blocks sodium and water retaining action of the naturally secreted aldosterone. Its diuretic action is utilised for the relief of oedema, associated with C.C.F., cirrhosis of liver and nephrosis.

There are two other steroid compounds—*dexamethasone* and *triamcinolone*, which, in doses of 1-2 mg/day, have been found to relieve oedema, resulting from the mineralo-corticoid therapy and can profitably be used in such cases.

Assay: The corticoids can be assayed both by (a) *Biological* and (b) *Chemical tests*, as outlined below:

(a) Study of the *survival time* in adrenalectomised animals after administration of cortical extracts or any other preparation, in comparison with the control, as well as, any standard preparation.

(b) *Eosinopenia test*: following the same principles as for all the assay methods of similar types.

(c) *Paper chromatography* method: for estimation of the test drug.

Metabolism: *Absorption.* It is variable and depends upon the preparations used.

(a) Cortisone and hydrocortisone are effectively absorbed per OS/IM.

(b) DOCA has satisfactory absorption from IM inj. but much slower from S.C. implants and inadequate from the oral and sublingual uses.

Fats and excretion: about 80% of the hormone is degraded in liver and excreted in conjugated forms and about 20% is excreted in urine as 17-ketosteroids. This is used as an index for adreno-cortical function.

Actions: (a) The corticoids show many revealing physiopharmacologi-

cal actions in respect of the following: (a) Homoeostasis, (ii) Body fluid regulation, (iii) Mobilisation of energy for cellular work etc.

(b) They also sometimes show mutually opposing and overlapping actions amongst the individual members of the 3 groups of corticosteroids and with other hormones as well.

Carbohydrate metabolism: (a) There is a distinct diabetogenic action, comprising hyperglycaemia, glycosurea, decreased glucose oxidation, increased resistance to Insulin, increased liver glycogen deposition and also neoglycogenesis. (b) Hydrocortisone is the most active in this respect and others, in decreasing order, are: Cortisone, \rightarrow Corticosterone \rightarrow aldosterone and \rightarrow DOCA.

Fat metabolism: (a) Every phase of fat metabolism: Oxidation, synthesis, mobilisation and storage, is influenced by cortisone and related glucocorticoids, (b) It is properly deposited in the body and ketonaemia, as well as ketonuria, are reduced, (c) The distribution of fat affects neck, supra-clavicular area and cheek, producing what is known as *buffalo hump* and *moon face*.

Antianabolic action: Proteins and fats are catabolised rapidly, for formation of glucose and this results in wasting of muscles and osteoporosis.

Electrolytes and water metabolism: (a) In hypocorticism, there is sodium loss, hyponatraemia, hyperkalaemia and shrinkage of extracellular fluid, with cellular hydration. The opposite occurs in hypercorticism.

(b) There is an enhanced reabsorption of NaCl and H_2O , with increased excretion of K from tissues, as well as tissue fluids. Mineral derangements of Addison's disease are completely reversed. In the descending order of this activity: Aldosterone, \rightarrow DOCA \rightarrow Corticosterone \rightarrow Hydrocortisone and \rightarrow Cortisone, may be placed. 11-dehydro corticosterone is completely devoid of this activity.

(c) Aldosterone is 25 times more potent than DOCA in its action on NaCl retention but only 5 times as active, in promoting K excretion.

RELATIVE ACTIVITIES

Steroids	Glucocorticoid activity	Mineralocorticoid activity
	Cortisone representing --100.	(Na/K ratio in urine of rat) DOCA representing 100
DOCA	1	100
Corticosterone	50	14
Cortisone	100	6
Hydrocortisone	155	8
Aldosterone	—	10,000

Inflammatory processes: The action is complex and sometimes even conflicting, in view of the interplay of peripheral groups of corticoids. Though glucocorticoids are considered to be *anti-inflammatory* and mineralocorticoids *proinflammatory*, actions are sometimes mixed up together.

(a) The glucocorticoids suppress inflammatory responses to the hypersensitivity reaction or infection. Vasodilatation, increased capillary permeability, diapedesis of leucocytes, movements of colloid particulates, are impeded. The *anti-hyaluronidase* action also subscribes to this improvement. And yet, dissolution of lymphoid tissues with release of globulin and also leucopenia occur. The former is concerned with the 'Immunity response'. The action of corticoids on the lymphoid tissue is definite, its insufficiency resulting in increased proliferation, with relative lymphocytosis, while in Cushing's syndrome, there is the opposite effect. ACTH and cortisone produce maximum effect in this respect and DOCA none. ACTH and cortisone also reduce the eosinophil count, which is the basis of the *eosinophilia test*, in the diagnosing the adrenocortical insufficiency. The mechanism of the immunity response is not yet definitely settled and it is not established as to whether this is due to the antiinflammatory action or to the circulating antibodies, antigen-antibody or hypersensitivity reactions. Corticosteroids and ACTH however, modify the clinical course considerably, to the benefit of the patients.

(b) Because of this anti-inflammatory action, glucocorticoids, used alone may flare up the activity of pathogenic organisms. Therefore, its use under the cover of an umbrella of antibiotics, is advocated. In the words of Hench, 'corticoids act like an asbestos suit, protecting the tissues from the flames but not from heat. The cause of the inflammation is not removed but the effect is suppressed. In severe toxæmias, the protection of tissues from bacterial endotoxine and in eye condition with devastating exudation and capillary proliferation, a very prompt suppression of the inflammatory processes, results.

Antiallergic reactions: Both ACTH and cortisone are potent antiallergic drugs. The antigen-antibody reaction is not prevented, the immunity reaction is not enhanced and yet there is a dramatic relief. Biogenesis of histamine may be diminished and tissue responses to available histamine i.e. the hypersensitivity response, is minimised.

Other actions: The following observations made with experimental and clinical studies with corticoids, may also be noted.

(a) Experimental *hypertension*, probably of renal etiology, involving the renin-angiotensin system, has been observed with DOCA. In *hypocorticism*, there are gross disturbances in the salt and fluid balances,

involving the circulatory system, which are appropriately corrected by this hormone. The corticoids also potentiate the *pressor responses* of epinephrine and in primary aldosteronism, there is marked hypertension.

(b) 11 and 17 corticoids, as well as cortisone, stimulate the C.N.S. and produce E.E.C. changes. In *Addison's disease*, there is depression of the C.N.S. and considerable apathy, improved by the 'cortisone therapy'. In *Cushing's syndrome*, there is a high incidence of neurösis.

(c) Cortisone also possesses *gastric hyperacidity*, as well as, *analgesic-antipyretic* actions.

(d) Depressed skeletal muscle function and *asthenia* seem to be due to the electrolyte imbalance, as well as from the defect of CH metabolism. Inadequacy of the circulatory system also subscribes to it. Cortisone, more than DOCA, improves this asthenia. The muscle weakness in *primary aldosteronism*, is however due to hypokalaemia,

Limitations: (a) Those of any *substitution therapy*. Relapses after discontinuation of the drug, often occur.

(b) Susceptibility to infections is increased and consequently they are to be used under the coverage of antibiotics.

COMPARATIVE TABLE

Name	Source	Action and uses
CORTISONE	Natural and synthetic	(a) A glucocorticoid with minimum action on the mineral metabolism. (b) Used in collagen and allergic disorders and as an antiinflammatory agent, mostly.
HYDROCORTISONE	—do—	Similar to cortisone but more potent and better suited for <i>local uses</i> , in skin, mucous membrane, conjunctiva and joint troubles.
PREDNISONE AND PREDNISOLONE	Synthetic	Actions and uses are the same as above but more potent. They are less effective, topically.
9-ALPHA-FLUORO HYDROCORTISONE	—do— ,,	Mineral and glucocorticoid actions and used as an antiarthritic agent.
DESOXYCORTICOSTERONE	—do—	A mineralocorticoid, par excellence, and more suited in Addison's disease.
ALDOSTERONE	Natural and synthetic.	(a) Action and uses are the same as of DOCA but 20-30 times more potent. (b) It does not induce hypertension and corrects carbohydrate and pigment metabolisms.

(c) On prolonged use, electrolyte imbalance, oedema, hypertension, androgenic effects and also endogenous ACTH and cortisone deficiencies, may occur.

(d) Other toxic effects are: (a) hyperglycaemia and glycosurea, (ii) perforation of peptic ulcer, if already present, (iii) myopathy, (iv) psychosis (v) osteoporosis and (vi) hypercoagulability of blood.

ACTH AND CORTICOID THERAPY

This is divided under *two* main headings:

- (a) Endocrinopathy with deficiency states.
- (b) A variety of unrelated disorders, improving after therapeutic hypercorticism, by ACTH or corticosteroids.

These drugs are *life-saving* and of special value in:

- (a) Addison's disease.
- (b) Severe burns.
- (c) Serum sickness.
- (d) A.R.F.
- (e) Status asthmaticus.
- (f) Exfoliative dermatitis.
- (g) Lupus erythematosus and
- (h) Periarteritis nodosa.

They are *effective* but *not necessarily life-saving* in: (a) Acute gout, (b) Leukaemia, (c) Hay fever (d) Urticaria (e) Nephrosis (f) Rheumatoid arthritis and (h) Inflammatory conditions of the eye.

Addison's Disease: Drugs of choice are: mineralocorticoids, supplemented by cortisone, if necessary.

In an *Ordinary case* (a) DOCA: 2-5 mg I.M., along with NaCl 5-10 gm./day. (b) After sabilisation, pellets of 100-200 mg/8 months. (c) If cortisone is necessary, the prescribed dose is 50 mg/day/O.S.

In *Addisonian crisis*: (a) Glucose saline I.V. drip and DOCA 10-15 mg. I.M. (b) Hydrocortisone 50 mg. I.V. followed by 10 mg./hr. till the crisis is over. (c) Thereafter treatment as in ordinary cases.

Excellent result and complete revolution in the prognosis of the disease, have occurred with the above line of treatment and patients can now lead useful ambulatory lives, as in the case of diabetes, these days.

Collagen Disease:

Rheumatoid Arthritis: ACTH or cortisone therapy is indicated. Cortisone 100 mg/day/O.S. For painful joints 0.5-2 ml. of *hydrocortisone*, intra-articularly, is used.

Acute rheumatic fever: Cortisone is used in very severe cases only. It shortens the course and suppresses or prevents the cardiac damage.

Acute gout: Though sometimes dramatic relief is produced by ACTH in 12-36 hours, it is not considered to be superior to *colchicine therapy*, in the majority of cases.

Lupus erythematosus: Periarthritis nodosa and scleroderma, improve by ACTH and cortisone therapies.

Allergic Disorders: Bronchial asthma and status asthmaticus, not responding to the usual treatment. *Cortisone* 50 mg, 25 mg/hr /8 hrs. 25 mg./6 hrs. for the first day. Thereafter, 10 mg./6 hrs., reduced to 25 mg./day. It is of little value in chronic asthma.

In V. M. rhinitis, drug allergy, Loeffler's syndrome, ulcerative colitis, regional ileitis and allergic dermatosis, there is some improvement but no cure is produced by these drugs.

Cerebral oedema: *Prednisone* 50-100 mg/day, is used for the suppression of the inflammation.

Leukaemias: It is most useful, because of its lympholytic action. It is used for acute granulocytic, lymphocytic and chronic leukaemias, for temporary palliation.

Inflammatory Conditions of Eye: (a) In *acute stages*, it produces dramatic relief of pain and hyperaemia, with mobilisation of exudates. (b) In *chronic conditions*, the response is slow and there are greater incidences of relapses. (c) *Topical application* is recommended for the *anterior segment* conditions viz iritis and keratitis and *systemic use*, for the *posterior segment* diseases like uveitis and choroiditis. (d) *Hydrocortisone* is preferred for *local therapies*.

Nephrosis and Infective Hepatitis: There is some effect from the 'cortisone therapy' and it is often used but the course of the disease is not much checked.

Hypopituitarism: ACTH 5-10 units/12 hr. I.M., but for the long range *maintenance therapy* *Cortisone* is to be preferred, as it does not inhibit pituitary activities.

Tuberculosis: Though initial reports indicated flaring up of the quiescent tubercular lesions after *cortisone therapy*, the consensus of opinion now is, that it can safely be administered in tuberculosis under an appropriate coverage of anti-tubercular drugs. It has no *in vivo* or *in vitro* action on the tubercle bacillus and it probably acts by modifying inflammatory responses or immunity reactions, in the patient. Though its distinct indications are in T.B. meningitis and in patients showing hypersensitivity to antitubercular drugs, it may also be beneficial in

(i) T.B. of serous membranes, (ii) Exudative and intractable chronic T.B., not responding to the usual treatment, (iii) Tuberculous empyema and (iv) Fulminating pulmonary tuberculosis.

MALE SEX HORMONES

Historical: (a) Testicular deficiency has been associated with *ageing* in man, from time immemorial and consequently, 'hormone therapy' has been used for *rejuvenation* purposes.

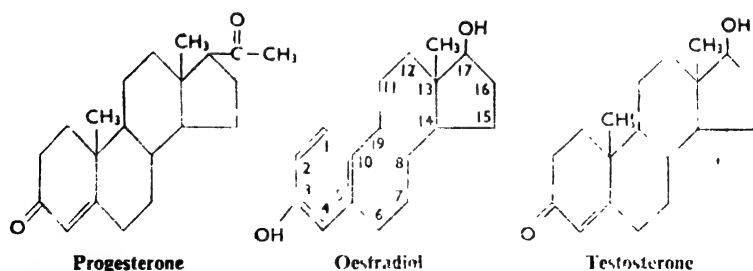
(b) Masculinising effects in hens from the transplantation of cock's testes, was demonstrated by John Hunter in 1771 and testicular grafting was made on himself, by Brown-Sequard in 1886, at the age of 86 years for rejuvenation purposes.

(c) Voronoff's operation with the grafting of monkey testes and Steinach's operation by the ligation of vas deferens, were introduced at a later stage, for the same purpose.

(d) Introduction of the *cock comb* and *seminal vesicle* bioassay techniques in castrates, for the dosage of testicular hormone and isolation of 15 mg. of androsterone by Butcnandt, from 15000 litres of male urine, in 1931 and its synthesis by him 2 years later, were the important steps in the progressive advancement of our knowledge in male sex hormones.

(e) Finally, *testosterone* was isolated and synthesised by Laquer and others in 1935 and was found to be 15 times more potent than androsterone and believed to be the real male sex hormone and others, its derivatives.

Chemistry: As stated earlier, the chemistry of sex hormones, is complex and there is a lot of similarity in the chemical nature of all the three steroid hormones. The male sex hormones are steroids, having



Illus. XXXVII: Chemical similarity of sex hormones

a basic cyclopentanoperhydrophenanthrene ring, with a CH or SO group at position 3. Esterification of androsterone prolongs its

action, while its reduction to androstenediol, doubles or trebles its potency. On comparing the male and female sex hormones, it is observed, that in *oestrones*, the first ring is unsaturated and in the *male sex hormone*, an additional CH_3 group at position 13, is present. The chemical nature of the male and female sex hormones, is shown below:

Preparations: *Testosterone* 3-6 mg. tablets and 75 mg. pellets. *Testosterone propionate*, an oily solution containing 10-50 mg/ml. *Aqueous suspension* 25-50 mg/ml. *Methyl testosterone*: Tablets of 5 or 10 mg and oily solution containing 50-100 mg/ml.

Metabolism: (a) It is readily absorbed from the *G.I. tract* and inactivated by the liver.

(b) Methyl testosterone is not inactivated and can be given orally or sublingually.

(c) Testosterone in oil, is quickly absorbed after I.M. inj. and the crystalline suspension is completely absorbed in 7 days.

(d) 40 per cent of the drug is degraded in the body to less active androgens or inactive steroids, in the liver and then excreted in urine as 17-ketosteroids.

Actions: (a) Masculinisation of females, increased growth, development of genital organs, promotion of secondary sexual characteristics and descent of testes, are the important physiological actions of testosterone.

(b) The effects of *castration* comprise atrophy of seminal vesicles, prostate, penis and reduced libido. All these are counteracted by the hormone.

(c) It does not produce any *aphrodisiac action* and there is no stimulation but maintenance of 'spermatogenesis'.

(d) Antigonadotropic and anti-oxytocic actions are also produced by the hormone.

Uses: The androgens find their uses in a number of conditions with hypothetical results:

(a) Hypogonadism, eunachoidism and counteracting the effects of castration. *Testosterone propionate*: 200 mg. every 2 or 3 weeks, for 2-3 years, or *testosterone propionate*—50 mg., thrice a week, or *methyl testosterone*—30-50 mg. daily.

(b) As an *oestrogen antagonist*, it is used in excessive uterine bleeding and in carcinoma of the breast. *Testosterone propionate* 25-100 mg. I.M., twice a week, is used.

- (c) In *cryptorchidism*, gonadotrophins are more effective than the androgens.
- (d) In *hypopituitarism*, methyl testosterone--10-20 mg., with 1 mg of diethyl stilboestrol, is used.
- e) In ageing, osteoporosis and menstrual disorders, it is sometimes tried but the results are unpredictable.
- (f) In refractory anaemia, 1.2 gm, per week, of testosterone ethanate, with 200 mg. of methyl testosterone, is sometimes used.

FEMALE SEX HORMONES

The two principal types are the *follicular* and the *corpus luteal* hormones.

OESTROGENS

- Historical:** (a) It has long been known that the removal of ovaries, resulted in the atrophy of uterus and loss of sexual functions. The nature of the hormonal control was established in 1900 by Knauer, when he found that this was prevented by ovarian transplants. Thus the existence of ovarian hormones, was realised.
- (b) In 1923, Allen and Doisy, developed a quantitative test for the bioassay of these hormones which facilitated their estimation. Their presence in blood was detected by Frank and associates, in 1925 and the urinary excretion of oestrogens during pregnancy, was discovered by Zondek, in 1928, which permitted Butenandt (1929) and Doisy et al (1929 & 1930), to isolate the hormone in crystalline form.
- (c) The role of *corpus luteum* was established by Baird (1897); Frankel (1903) and Allen (1929).

Physio-Pharmacological Roles: The oestrogens are primarily concerned with maturation of graafian follicles, under the influences of F.S.H. Their secretion is responsible for the development of genital tract and secondary sexual characters in females. They are obtained from the following three sources:

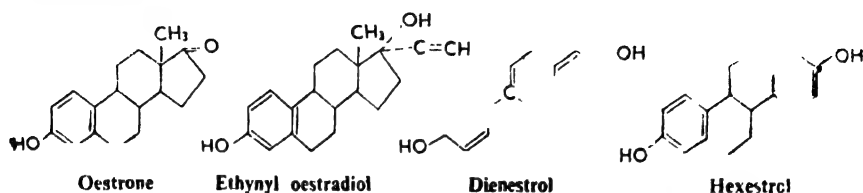
- (a) *Natural*
- (b) *Semisynthetic*
- (c) *Synthetic esters and conjugates*

The *natural oestrogens* are obtained from cattle ovaries, in which, they are available in a concentration of 1 gm/50 tons of ovarian tissues. Its concentration in the urine of *pregnant females*, is 10 times greater.

Of the three groups, the *natural hormones* are the most potent but

easily hydrolysed in the stomach. The *synthetic* preparations have the advantage of oral administration.

Chemical Nature: Of synthetic oestrogens, along with oestrone, is represented below:



Illus: XXXVIII: Chemical nature of synthetic oestrogens

The *synthetic oestrogens* are *stilbene derivatives* and comprise diethylstilboesterol, dienestrol, benzeestrol, hexestrol and ethynyl oestradiol.

Assay: This is carried out by the *vaginal smear method* in ovariectomised mice as detailed in the Chapter 6. The appearance of cornified and the nucleated cells, suggests oestrogenic effect, which is then compared with a standard preparation.

Metabolism: (a) The absorption of oestrogens is variable from the G.I. tract. The oily suspension, used I.M., produces more prolonged actions.

(b) They are degraded in the liver and excreted in bile, faeces and urine.

(c) The estimation of urinary 17-ketosteroids, forms a guide for the assessment of ovarian functions.

Dosage Forms: These are as under:

<i>Natural</i>	<i>Synthetic</i>
Oestradiol dipropionate: 1-5 mg/IM/day	Stilboesterol: 0.1-5.0 mg/OS and I.M./day
Oestradiol monobenzoate (Progynon): 1-5 mg/IM/day.	Dienestrol: 0.5-10 mg./OS/day.
	Hexoestrol: 1-4 mg/O.S.
	Eticyclin: 0.01-0.1 mg/OS.
	Mestibol: 0.5-1 mg/OS/day; or 10-25mg./IM/twice a week.
Oestrone: 1-10 mg/I.M.	Chlorotrianesene (TACE) 12-24 mg/OS/day
	Ethynyl oestradiol: 0.01-0.5 mg/OS.

Action: These are diverse in nature and not fully known, as yet. Besides the proliferation of myo- and endometrium, oestrogens stimulate uterine contraction and on prolonged use, may produce malignancy of breast and uterus. Further, 'oestrogen-androgen antagonism' is the basis of its use in enlarged prostate and of the latter in 'breast cancer'.

Toxicity: Nausea, vomiting and headache and also bleeding, tenderness and pigmentation of breast.

Of these, nausea is of frequent occurrence, particularly with the synthetic oestrogens. Along with anorexia, it may sometimes be very distressing to the patient, but the food intake is not affected and there is hardly any loss of body weight.

Uses: Numerous but not necessarily with predictable results in all conditions:

(a) Hypogonadism in females. (b) Dysmenorrhoea and functional uterine bleeding. (c) Postmenopausal troubles. (d) Enlarged prostate and malignancy. (e) Senile vaginitis or kraurosis (f) Induction of labour. (g) Hirsutism (h) Acne, (i) Osteoporosis (j) Prevention of heart attacks etc.

The selection of preparations is often made on *trial and error method* on the basis of individual experiences, not necessarily scientifically explainable.

Antioestrogens: Besides progestin, androgens and some of the weak oestrogens, *Chlortrianisene* (TACE) and *Clomiphene*, are endowed with antioestrogenic activity and have been used in infertility and menstrual disorders, in doses of 25-75 mg/day, for 5-10 days. Their *side-effects* are—(a) enlargement of ovaries (b) flashes (c) gastric upset and (d) skin rashes.

PROGESTERONE

Corpus luteum hormone is secreted under the influence of the leutinising hormone of anterior pituitary gland. It is found in *alpha* and *beta* forms.

Actions: They are not fully clear. In many respects, they are antagonistic to oestrogens and in some respects, complementary to such

other particularly, in cases of uterus and ovary. Progesterone makes the uterus insensitive to pitocin and is excreted in urine in the form of *pregnandiol*. A sudden fall in the *pregnandiol* level in urinary excretion, is indicative of *threatened abortion*, in pregnant women.

Preparations: *Progestrone* in oil 5-20 mg/day/I.M. *Anhydroxyprogesterone*: Tablets of 5-10 mg. and Injection of 10 mg/ml. *Ethisterone* or *luteocyclin* 25-100 mg/day.

Uses: (a) Threatened and habitual abortions, (b) Metropathia haemorrhagica, (c) Hyperemesis gravidarum.

THERAPEUTIC CONSIDERATIONS

Female sex hormones are still largely used for a number of gynaecological disorders with mixed results. These may be due to the unknown interrelationship in the functioning of these endocrines.

Menopausal Troubles: An inevitable transition characterised by irregular menses, vasomotor troubles, obesity and drift towards masculinity. These symptom complexes are due to decreased oestrogens and A.N.S. instability. It usually lasts for 1-2 years and is consequent to the loss of ovulation.

(i) *Oestradiol*: 1-5 mg. I.M. two inj./week. (ii) *Stilbaesterol*: 0.5 mg/OS. (iii) *Ethinyl Oestradiol*: 0.01-0.05 mg I.M./OS/day. (iv) *Sedatives*, as and when required.

The treatment is to be continued till the crisis is over. Vaginal smear may be indicative of the beneficial effect of the therapy, which is usually effective. There may sometimes be *withdrawal bleeding*. Small doses of androgens, along with oestrogens, have also been found to be satisfactory.

Habitual Abortion: There are diverse causes viz inadequate progesterone synthesis, uterine troubles and syphilis. 'Long term therapy' is to be considered and the following may be tried as a routine measure.

(a) *Progesterone* 20 mg/day, (b) *Diethyl stilboesterol*: 5 mg/day 2 week³. Their uses are based on the principle of oestrone provoking progesterone secretion. Vitamin E is also used whatever might be its ulterior value, the treatment of underlying etiology is also necessary.

Oestrogens of the type of *progynon* are also sometimes used as abortiflying agents in the earlier part of pregnancy. The result is equivocal.

In cases of *threatened abortion*, as also in the *toxæmia of pregnancy*, certain abnormalities in the urinary excretion of oestrogen, *pregnandiol*

fall and chorionic gonadotropin, are in support of the treatment with diethyl stilboesterol. However it is not a dependable therapy.

Amenorrhoea: This may be due to the *primary ovarian failure, secondary* to pituitary and thyroid deficiencies or some subnormal health conditions. *Diethyl stilboesterol:* 3.5 mg/day, for 20 days, before the expected period and *progesterone* for 5 days during or after the period, constitute 'Kaufmann's method of treatment', with mixed results. As the condition is due to some primary ovarian failure, treatment has to be continued for sufficiently long time. The associated hypopituitarism, deficiencies of thyroid and adrenal cortex, have also to be considered and the therapy directed towards their rectification.

Functional Uterine Bleeding: When progesterone is not available, *diethyl stilboesterol:* 1-10 mg/2-4 hrs., is given, until the bleeding is controlled and then 5 mg/day is given for a week. Withdrawal bleeding should be expected.

Dysmenorrhoea: Its incidence is much on the increase, in the present social set up and mental make up of young women. It may be due to oestrogen-progesterone imbalance, uterine malposition, ischaemia and a low threshold for the tolerance of pain. *Experimental dysmenorrhoea* is reproducible by the use of *pitressin* and also by stretching the cervix and uterus.

Its management comprises the following:

During attack: (a) Bed rest and use of electric pad.

(b) Sedatives and analgesics—phenobarbitone 30 mg. with aspirin 0.3 gm/3 hourly and

(c) Spasmolytics—atropine, mydrindon, transentin.

During interval period:

Hormone therapy with (a) Diethyl stilboesterol 1 mg. at bed time.

(b) Progesterone 5-10 mg. I.M. or 2-10 mg/OS, for diminishing uterine contractions and

(c) Methyl testosterone 5 mg. sublingually, daily, is recommended.

The correction of the malposition by DC and use of passaries, are essential and the use of some of the vegetable drugs—ashoka and abroma, are also advocated.

Lutrexin: A water-soluble, *nonsteroid* uterine relaxing factor, isolated from ovaries, relieves the pain of dysmenorrhoea in 70%-96% of cases and has an 'antipitressin action'. It is also used to sedate the uterus in premature labour. *Dose:* 2.5 mg/kg.

CHAPTER

55

CONTRACEPTIVE AND ANTIFERTILITY AGENTS

POPULATION EXPLOSION. NEED OF BIRTH CONTROL IN DEVELOPING COUNTRIES. MEASURES AND DEVICES. SCOPE AND LIMITATION OF ANTIFERTILITY MEDICATION

[Mounting socio-economic problems emanating from unlimited parenthood, have guided human inquisitiveness to find out birth control measures from the earliest day of our social history. Coitus interruptus, timed abstinence, use of crude mechanical and chemical devices, have been in use, in spite of lack of knowledge of the exact mechanism of conception. The work of Malthus, Dawson, Annie Besant, Sanger, Marie-Stopes, Freud and others, have been instrumental in introducing birth control consciousness, clinics and associations, all over the world and various types of contraceptive devices—spermaticides and operative measures, introduced in this century. India also has undertaken a gigantic programme of Family Planning at Central and State levels, after independence.]

Our knowledge of hormonal control of ovulation and conception, developed during the past 50 years, has permitted the discovery of hormonal drugs of oestrogen-progesterone series during the past 1 or 2 decades. These drugs act by creating hormonal imbalance, preventing ovulation, conjugation and/or nidation of the fertilised ovum. Several of these preparations like *Enovid*, *Ovulen*, *Anovlar* or *Ortho-novum-58*, which are predominantly oestro- or progesteronic in nature and used in *combined* or *sequential therapy*, have been accepted by the Birth Control Association and recommended for use. They are effective, little toxic and selective in action. The remote impact of created hormonal imbalance, caused by these agents, from prolonged uses of 30-40 years and their constitutional side-effects have yet to be assessed over a much longer period than at present.]

General Considerations : 'Family Planning' or *Planned Parenthood*, having not more than 2-3 children in a family, is *the cry* of the day, and more so, in developing countries than the developed ones, in which, population has more or less been stabilised.

The world population, though unequally distributed, is at present estimated to be 300 crores. A baby is born every $1\frac{1}{2}$ second, 57000/day and 21 million/year, while the death rate/year is 8 millions, adding 13 million/year to the above population, of which, the major share is of the underdeveloped countries.

It took 0.5 million years for the earth to have the present population, which at this rate, may double up in the next 35 years, become quadruple in the succeeding 25 years and reach 20,000 crores or 64 times, in a century.

Historical Background: The concept of Family Planning is not a new contribution of recent years only. It has existed and been followed in some form or other, throughout the history of our organised societies. Such procedures as *Coitus interruptus*, *abstinence*, use of ordinary or medicated *linens* or sponges, intercourse during certain periods of intermenstrual interval, have been practised. The issue however, received increased attention from the end of the 18th and more particularly, from the latter half of the 19th century.

In 1798, Malthus brought forward his challenging concept, known as '*Malthusian Theory*', according to which, the population of the world always grew in geometrical progression, while production of food was increasing only in arithmetical progressions. The concept made its impact on the intellectuals of the 19th century and gradually the need of family control and planning, started being realised. Thereafter the *Malthusian League* and other organisations started being organised in different countries, creating family planning consciousness. The work of Annie Besant, Marie Stopes, Sanger, Lord Dawson and Sigmond Freud, gradually lifted the veil of orthodoxy and introduced *birth control measures* and *clinics* in every country. Amongst the developing countries, India was one of the first to launch her National Family Planning Programme at Central and State levels, from 1953 onwards.

The *contraceptive measures*, actually in use, are of *two types*:

1. *Contraceptive devices*
2. *Oral contraceptives*

1. CONTRACEPTIVE DEVICES

The various procedures for prevention of fertilization, in use, are (I) *Modified methods of coitus*. (II) *Mechanical devices* (III) *Chemical Spermatocides* (IV) *Intra-uterine devices* and (V) *Surgical measures*.

Modified Coitus: In different forms, and also the *rhythm method*, based on the discovery of *mid-cycle phase of ovulation* and withholding of intercourse from the 11th to 19th day, during which, the conceptions were more likely to occur. Both these methods are cumbersome, not absolutely sure and not free from causing some mental tension.

Mechanical Devices: They comprise the use of *condoms*, *vaginal diaphragms*, and *cervical caps*, of which the first probably, is the most frequently used by the young couples, all over the world.

Chemical Contraceptives: They comprise use of local spermaticidal antiseptics—permanganate lotion, dettol, hexyl-resorcinol, chiniosol, p-tri iso propyl phenoxy polyethoxy ethanol, which are used as *tampon* or as *vaginal douches*. Similarly, *foams*, *aerosols*, *effervescent tablets*, *koromex jellies* are also used for spermaticidal purposes. They are not always effective besides their messiness in the procedure of application.

Intra-Uterine Devices: (I.U.D.) Though recently introduced in the present form, they have a lengthy history in other forms e.g.—*Casanova's gold ball*, *Gutta Macher's* rubber spirals, pessaries, commet, otering and finally, now, *Lippy's loop*. Here again the procedure is cumbersome, result not always dependable and some *side-effects* not infrequent.

Surgical Measures: These are mainly two—(a) *Vasectomy* for *males* and (b) *Tubal tying* (T. T.) and tubectomy for *females*. The operations are fairly simple and the second is usually carried out as a part of the *post-partum programme*. The results obviously, are highly satisfactory and after-effects, from the experiences so far gained, are not deleterious. The *ovarian cycle*, as well as menses continue and so is the case in males, in respect of *spermatogenesis* and *testicular interstitial cellular functionings*. The cells are destroyed intra-luminally and future conceptions do not occur.

2. ANTIFERTILITY DRUGS

A group of *hormonal drugs* belonging to the series of *oestrone* and *progesterone*, which given in *combined* or *sequential order*, disrupt hormonal equilibrium, ovulatory cycle and the fertilisation of ovum. This new approach for dealing with physiological problems by physiological means with further prospects in future, has completely revolutionised the 'superfertility problem' and opened a novel line of control of this knotty problem.

Before going through the *drug therapy*, itself, it may be advisable to briefly refresh our knowledge of the physiology of conception, to appreciate better the concepts of hormonotherapy and their *modus operandi*, as *oral contraceptives*.

Physiology of Conception: This presupposes the considerations of the physiology of (a) Ovulation with secretion of oestrogen and progesterone. (b) The menstrual cycle with its ovarian and uterine components, as also (c) The role of the recently introduced prostoglandins as accessory factor, facilitating the fecondation.

The ovarian cycle starts under the influence of F.S.H. which promotes the growth of 20 premordial follicles, of which only one is destined to be the functional ovum for each menstrual cycle. This singly chosen *follicle* comes to staggering prominence from its excessive growth, from increasing secretion of *oestradiol* and is known as *graffian follicle*.

Towards the middle of the cycle, there is increased secretion of L.H. This ripens the follicle which then ruptures at about the 14th day. *Ovum* is shed and the cellular mass left over, is termed *corpus luteum*, which secretes progesterone. The corpus luteum starts degenerating between the 24th—28th day, thus bringing down the progesterone= oestrogen level. This, in turn, causes the liberation of tropic hormones from anterior pituitary, which stimulate the secretion of ovarian hormones. When sufficient amounts have been secreted, the tropic hormones are produced less, by the *feed-back* mechanism.

Side by side, the *uterine cycle* also proceeds. The uterine endometrium responds to the ovarian hormones. At first, it grows under the influence of oestrogen. This is the *proliferative phase*. During this, *epithelial*, as well as *glandular* elements increase and the *mucus* secreted is *watery*.

During the *second phase*, the fully mature glandular elements start functioning and this is called the *secretory phase*. The *mucus* becomes *viscid* and *scanty*.

Finally, just before menstruation, both oestrogen and progesterone are withdrawn and the newly formed endometrium is shed off and the whole cycle is repeated. On the contrary, if per chance, conception has occurred, the corpus luteum persists and goes on secreting progesterone till the placenta is matured enough, to do the same and thus the endometrium is saved from being shed. In *anovulatory cycle*, no corpus luteum and no progesterone is formed and the secretory phase does not occur. Upon withdrawal, endometrium again sloughs, but erratically, over a prolonged period, with much more bleeding.

In substance three clear-cut phases are (a) Stage of endometrial proliferation and repair, by oestrogen (b) Progestational secretory phase by progesterone and oestrone (c) Destructive phase and menstrual flow from loss of support from both.

Prostaglandins: These are the derivatives of *prostanic acid*, synthe-

sised in tissues from essential *fatty acids*. Van Euler discovered it in human seminal plasma in 1935 and thereafter, several closely related substances of lipid nature, have been obtained from various tissues and biological fluids, which are not all exactly identical in all their biological responses to different tissues and species of animals, some even showing effects opposite to each other.

There seems to be unanimity of opinion as regards their involvement in the *motility of sperm and ovum*, as also in the motility of female reproductive organs and fertility. Some of their other actions are (a) G.I. motility, (b) Bronchodilatations (c) Lowering of B.P. and (d) C.N.S. depression, in individual cases.

They seem to play important roles in the physio-pathology of conception, parturition, dysmenorrhoea and menstrual disorders. They deserve further studies for elucidating their real status and role, on the functioning of female physiology.

In summarising what has so far been discussed on the physiology of conception, one may conclude that, the predominant role of *oestrogens* is to inhibit the secretion of FSH, while, the continued effect of *progesterone*, is to inhibit the release of L.H. (b) Ovulation could thus be prevented by both of them. (c) The effect of the *oral contraceptive mixture*, as will be seen later, is more directly on the *ovary*—the *oestrogen component* inhibiting ovulation and *progestin* controlling *withdrawn bleeding*. (d) They may also interfere with the impregnation and nidation of the fertilized ovum by their direct action on the genital tract, which has to be in an ideal condition for the same. (e) Similarly the watery secretion of the cervix at the time of ovulation, is facilitatory, while the tenacious mucous secretion by progesterone is antagonistic to the viability and sojourn of the sperm. (f) Further, the transport of the sperm by the subtle movements of the cervix, uterus and fallopian tubes, are also necessary. (g) The role of prostaglandin in this part of the work, also appears to be very important. (h) All these prove that a very correct hormonal environment is essential for a successful conception.

Evolution of Antifertility Drugs: This had its basis on the knowledge of the physiology of conception, referred earlier and the role of the hormonal control in the *pituitary—ovary axis* and its *feed-back* system of working, as revealed by the work of Beard (1897) Fellner (1912), Moore and Price (1932), Sturgis and Albright (1940).

By then, different *oestrogenic preparations* and derivatives were available and the problem of availability of large quantities of *progesterone* from the vegetable sources of *yam*, was solved by the *Syntax*

Laboratory of Mexico. *Ethisterone* and *nor-ethisterone* were successfully prepared for oral administration and the combination of progesterone, nor-ethinodrol and mestranol, was marketed as *enovid* by the *Seattle Company*, in 1957 and accepted by the 'Family Planning Association of Great Britain', in 1960. In 1963, Voldzider introduced the *sequential regime* of oestrogen alone for a part of the cycle, followed by oestrogen-progesterone therapy, towards the end, in the contraceptive procedures. All these brought us to the present state of our knowledge of *oral contraceptives*.

Preparations: There are numerous, mostly synthetic and of proprietary nature, with predominant oestrogenic, progestational or combined effects, which latter, are mostly used and the former, for sequential therapy only. The oestrogen preparations, have as basis one of the synthetic *steroids*, like 'ethynyl oestradiol', diethyle stilbesterol and the progestational compounds are 17 1-hydroxy progesterone caproate, megestrol etc., which latter, is an active progestrial steroid, devoid of oestrogenic and androgenic effects.

In actual practice, mixtures containing both progestrogens and oestrogens as approved by the Family Planning Association, are used in the form of propirietary preparations, taking mestranol, ethynylestradiol and ethynylestranol as oestrogenic, while norethindrone, norethindrol, ethynodiol diacetate, norethisterone, nor-ethindrone and mesestrol acetate as progestational in varying proportions. The proprietary preparations actually used in Family Planning work, are:

ENOVID	(Mestranol + Norethynodrel)
ORTHO-NOVUM	(Mestranol + Norethindrone)
OVULEN	(Mestranol + Ethynodiol diacetate)
ANOVLAR	(Ethynyl estradiol + Norethisterone)
VOLIDEN	(Ethynyl estradiol + Megestrol acetate)

Ortho-novum SQ contains 0.08 mg of mestranol and 2 mg. of norethindrone and is used in 'sequential form' of therapy, mostly.

Of these, *ovulen*, containing ethynodiol diacetate, a progestational steroid, produces antiovolatory effect by inhibiting the gonodotrophic activity. The presence of 3 hydroxyl in place of keto-groups, imparts oestrogenic activity of about 3% of oestrone. It has the advantages of low dosages and toxicities. Of the available ovulation inhibitors, it is one of the most potent preparations for clinical use.

Enovid is a combination of nor-ethynodral and mestranol and of norethindrone and mestranol. They are 100% antiovolatory agents

and have minimum effects on menstruation and subsequent cycles. Administration of enovid may soften the os which should not be taken as an indication of early conception. Lactation and premenstrual tension are decreased or even stopped. Enovid produces essentially an oestrogenic response on the vaginal smear, in contrast with the progesterone like appearance of the smear after nor-ethinodrone or its acetate salt. Norethyndrel has high progestational and slight oestrogenic activity.

Side Effect: Though numerous, yet not of very serious consequence. However, remote consequences of a prolonged therapy has to be in mind, in long range plan, including tetatogenity, which at present, is believed to be absent.

Mild: (a) Nausea, headache, mastalgia and oedema—needing lower oestrogen level.

(b) Psychological changes—increased or decreased libido (50 %, 40 %).

(c) Withdrawal bleeding may be absent, which may be confused with pregnancy. It is more common with combination therapy and may be corrected by changing to sequential therapy. These side-effects usually do not require discontinuance of the therapy.

Moderate: (a) Break-through bleeding from inadequate doses of progestin. It may be eliminated by a change to combination therapy.

(b) Androgenic side-effects—weight gain, hirsutism and acne.

(c) Patches of skin pigmentation, specially in dark skinned women, aggravated by sunlight exposure and vitamin deficiency. It is usually reversible on discontinuance.

(d) Prolonged amenorrhoea and infertility on discontinuance in women with menstrual irregularities.

Severe: (a) Impaired liver function and jaundice (b) Hypertension

(c) Thromboembolic disorders—thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Frequency of incidence: First cycle nausea—maximum of—25%; Breast discomfort—13%; Weight gain—5%; Breakthrough bleeding—5.2% and Amenorrhoea—3.6%.

<i>Comparative effectivity</i>	<i>Continued therapy</i>	<i>Interrupted therapy</i>
Pill	0.5	1.5
I.U.D.	1.7	6.5
Condom	6.0	15.0
Diaphragm	11.0 s	30.0
Rhythm	14.0	32.0
Chemical	10.0	42.0

Mode of Use: Two methods (a) *Combination therapy* (b) *Sequential therapy*.

In *Combination therapy*—oestrogen and progestin are given throughout the administration period of 20-22 days. Simultaneous presence of both the hormones is unsuitable for implantation, as follicular growth is inhibited by oestrogen and ovulation by progestin. The early presence of progestin also alters cervical mucus and tubal motility, so that, sperm and ovum union is impeded.

In *Sequential therapy*—oestrogen is given during the first part of the administration period and progestin is added during the last five or six days. In this, the contraceptive mechanism is in oestrogens causing inhibition of follicular growth.

Further Scope: The present regime of treatment, not being flawless, several other regimes are under investigation.

1. *Depot Therapy:* I.M. or S.C. implantation of long acting oestrogen and progestin, may one day supercede the existing daily dosage.
2. *Continuous low dosage progestin therapy:* Not to prevent ovulation completely but the hormonal rhythm of menstrual cycle, thus eliminating or diminishing oestrogen induced side-effects.
3. *Post-coital oestrogen therapy:* for 4 or 5 days of oestrogen therapy following coitus. This is promising and would be good in persons with low co-habitation rates and in rape cases.

Caution: (a) The therapy is recommended in highly fertile couples with anxiety about fertility control. (b) It is not recommended in adolescent girls, in whom epiphyseal closure has not occurred, nor in women with oestrogen sensitive tumours. (c) It should be avoided or used with caution in diseases, like—liver disorders, migraine, diabetes melitus, congestive heart failure, hypertension, thromboembolic disorders and also in those with familial history of breast and cervix cancer.

The use of *antifertility hormonal drugs*, is a recent development and has been found to be the best and easiest for use. They act by producing ovulatory and progestational hormonal imbalance and have to be used for years, throughout the period of 'fecundity' in the women. This poses the important question of affecting the normal physiological hormonal interaction with use of oestrogen and progesterone. It is known that the hormones have a very complex mechanism of working directly, indirectly and also by a type of interlinked reactions. The present study has to be continued for a longer period, to be able to assess more accurately, the salutary or non-salutary actions of these drugs, in their ultimate analysis. Whatever may it be, it is a great discovery and even in the latter eventuality, further discoveries will meet with the hurdles that may arise. This is how progress in science is achieved.

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SECTION

XII

MISCELLANEOUS AGENTS

CHAPTER

56

PHARMACOLOGY OF MISCELLANEOUS THERAPEUTIC AND DIAGNOSTIC AIDS

(a) IRRITANTS, COUNTERIRRITANTS, CAUSTICS, KERATOLYTICS, MELANISING AND DEMELANISING AGENTS (b) NOXIOUS GASES (c) MISCELLANEOUS DIAGNOSTIC AND ACCESSORY THERAPEUTIC AIDS (d) INDIGENOUS MEDICINAL PLANTS

[Besides the drugs so far studied in systemic pharmacology, there are still others acting on the skin and mucous membrane, as irritants, counterirritants, caustics and melanising agents. There are also noxious gases of toxicological importance, needing therapeutic aids. Finally, elementary pharmacology of diagnostic agents and indigenous medicinal plants, are included in this chapter as miscellaneous therapeutic and diagnostic agents.

The skin and *mucous membrane*, constituting the outer and inner coverings of the body, are not only endowed with many physiological functions but are also more easily exposed to toxic hazards. The *sudorifics* increase cutaneous perspiration, the *anhydrotics* are used for combatting the same; the *depilators*—X-ray, barium sulphide and thallium, remove hair shafts and even follicles, facilitating the treatment of certain skin diseases and also for personal hygiene. The *demulcents* and *emollients*, soften the skin and mucous membrane, in cases of irritation and injuries; the *counterirritants* relieve inflammation and pain by *axon-reflex*, the *melanising agents* are used in cases of depigmentation of the skin, as in leucoderma, while monobenzene, a hydroquinone derivative, is applied locally, for removing *hyperpigmentation*.

Amongst the *noxious gases* and vapours, *carbon monoxide* poisoning is combatted by O₂ therapy, blood transfusion and small doses of methylene blue. *HCN poisoning* by sodium and amyl nitrites and sodium thiosulphate; benzol and gasolene intoxication by supportive therapies and finally, CCl₄ toxicity, by liver protectives.

As *diagnostic aids*, for radio opaque contrast media, barium sulphate, water soluble and insoluble iodine compounds and iodophthalein are used for X-ray of the G.I. tract, bronchial tree, fallopian tube, blood vessels and pyelography.

As *diagnostic tests*, neostigmine, histamine, phenolamine, bacterial proteins and toxins, are used. Similarly, for assessing the functional integrity of certain organs, Evans blue, indocyanine green, sulphobromo-phenolphthalein and inulin are sometimes used.

As *accessory therapeutic measures*, the place of hydro and physiotherapy is important, particularly the latter, as it can be made available to patients, much more easily.

Of the large number of medicinal plants, growing in India and used in *indigenous medicines*, those like Rauwolfia, Kurchi and Ispaguhl, are already established and many others, are under investigation. It is probable that when the work is more systematically carried out, several C.N.S. and C.V. drugs, diuretics, antidiabetics, bronchial antispasmodics, anthelmintics and uterine sedatives, may either be found out from these sources or newer chemical structures, enlarging the scope of drug synthesis, discovered.]

It may be useful to go through a few miscellaneous topics not hitherto covered in general and systemic pharmacology. They are useful adjuncts to therapeutics and toxicology. They have specific purposes to fulfil and will be studied in a general manner in this chapter, under different heads.

I. DRUGS ACTING ON SKIN AND MUCOUS MEMBRANE

Physiological Considerations: As external and internal coverings of the body, the skin and mucous membrane, are important structures with many functions of their own:

- (a) Regulation of body temperature through V-M control and evaporation of $1\frac{1}{2}$ a litre of water and waste materials, daily and also reflex regulation of respiration through sensory nerve endings, in the skin.
- (b) Synthesis of vitamin D from sterols by U.V. rays and the antibacterial action of lysozyme, present in the skin.
- (c) Selective permeability for absorption and excretion of drugs and chemicals.

A large number of drugs act *locally*, on these structures, in a purely mechanical, physical or chemical manner. As their effects are mostly confined to the site of their application, their pharmacological properties warrant only a brief discussion. The drugs which act *physically*, are the demulcents, emollients, protectives, adsorbents, and absorbable haemostatics, while those acting *chemically*, are the astringents, irritants, sclerosing agents, caustics, keratolytics, antiseborrhoeics, melanising and demelanising agents and also some of the locally acting *enzymes*, used as *surgical curettes*. Several of them, have already been studied in other chapters and the rest will be briefly reviewed here. For the sake of convenience, a few other groups of agents viz.

sudorifics, anhydrotics, depilators and hair tonics, will also be studied, in this section.

SUDORIFICS

These increase cutaneous perspiration by diverse mechanisms:

- (a) Peripheral vasodilatation as by hot-bath, alcohol, Dover's powder and analgesic-antipyretics.
- (b) Stimulation of vagal endings by pilocarpine.
- (c) Stimulation of spinal and other centres, as in anxiety states, during emesis and also by camphor and ammonia.

Uses: Formerly many, as in pyrexia, oedema, uraemia, chronic skin diseases etc. but at present, they have hardly any therapeutic uses.

ANHYDROTICS

They produce the opposite effect and reduce or inhibit cutaneous perspiration. Atropine, talc powder, adsorbents and astringents are used for excessive localised perspirations.

DEPILATORS

These agents are used for removing hair from the body for better penetration of drugs in skin diseases and also as hygienic measures.

X-ray, in sufficient dosage, produces a temporary fall of hair, after a latent period of 19-24 days.

Barium, calcium and strontium sulphides dissolve hair shafts, which then break off, at the surface of the skin.

Thallium acetate, 8 mg/kg, is an effective depilator for the removal of hair from the scalp, in about a fortnight. Though reasonably safe for children, it is toxic for *adults* and has to be used with great caution.

HAIR TONICS

Theoretically, cantharis, pilocarpine and many other drugs are reputed to possess this action but in practice, they produce placebo effect, if the physiology of hair has not been attended to, in time.

DEMULCENTS

These are substances of high molecular weight e.g. gums, mucilages and starch, producing protective coatings against irritants, when used

as lotions, poultices or dressings. Important members are the following:

Gums: These are of two types: (a) *gum acacia* (b) *gum tragacanth*. They are obtained from different varieties of gummiferous trees—*Acacia senegal* and *Astragalus gummifera*, as exudates, after incision of the stem. The former has more binding and emulsifying properties and the latter is more fibrous in nature.

These gums when dissolved in water, form *mucilages* of different strength. *Dose:* 4-16 ml. *Pulv. tragacanth Co.*, comprises both the gums. *Dose* of 0.6-4 gm. They are used as suspending and emulsifying agents and also as a basis for demulcents and lozenges. *Vanilla* flavoured acacia syrup—10%, is used for making pharmaceutical preparations. Its use as gum saline has been discarded, because of the occurrence of *arabiosis* with spleno-hepatomegaly and hepatic failure:

Glycyrrhiza: or liquorice, the peeled roots of *glycyrrhiza glabra*, is a brownish-yellow powder. *Dose:* 1-4 gm.

Preparations: (a) Extr. Glycyrr. 0.6-2 gm. (b) Extr. Glycyrr liq. 2-4 ml. (c) Pulv. Glycyrr. Co. 4-8 gm. and also Syrup of Glycyrrhiza.

It is a sweet demulcent, which disguises the bad taste of drugs and acts as a laxative and expectorant. Of late, it has been found to have *cortisone type* of activity and is being used in: (a) Rheumatoid arthritis and (b) Peptic ulcer.

Glycerine: It is a sweet hygroscopic, syrupy liquid, obtained by the hydrolysis of fats and fixed oils. *Dose:* 4-8 ml.

- (a) It is a demulcent and emollient, which penetrates the skin, keeping it soft.
- (b) It acts as laxative, nutrient excipient and as vehicle for pills, pessaries, jellies and lotions.
- (c) The official glycerinum preparations are: (a) glycerine suppositories and (b) glycerine with aqua rosae, which are used as evanescent and soothing agent in herpes and eczema, respectively. The latter keeps the skin moist and prevents cracking.

Mel depuratum: or purified honey, is a good source for reducing sugars and vitamins and is used as a nutrient. It relieves the dryness of mouth and enters into several pharmaceutical preparations viz. *oxymel scilla* and *mel boracis*. It is also used as a vehicle for the administration of powders to babies.

Propylene Glycol: A clear, viscous liquid completely miscible with water, dissolving many essential oils. It is used as a solvent for many oral and injectable drugs and is also employed in cosmetics, lotions and hydrophilic ointments. *Polyethylene glycols*, are polymers of different molecular weights—150-700, in liquid form and 1000-10000, in solid forms. They behave like beeswax and hard paraffin respectively and are used in ointments.

EMOLLIENTS

These are the fats, oils, waxes and soaps, which lubricate and soften mucous membrane. Some of them also act as vehicles for ointments. The following are the important ones:

Olive Oil: A bland non-irritating, vegetable oil, having a dose of 15-30 ml. It is used as:

- (a) Nutrient, laxative, mild antacid and demulcent for poisons.
- (b) It forms the basis for liniments and lotions.
- (c) With 5% phenol, it is used at the stage of desquamation of skin, in smallpox and scarlet fever.
- (d) *Liquor calcis* (lime water—1, oil—2 parts), is a soothing agent for burns.

Paraffins: These are hydrocarbons, obtained from petroleum. They are available in two forms. (a) *Paraffin durum* and (b) *Paraffin liquidum*. The former is again available in two forms—(a) *flavum* and (b) *album* (bleached) and is used as a basis for ointments. The latter is used as an emollient laxative, in a dose of 7.5-30 ml.

Lard: or *adeps*, is the omental fat and *adeps lanae* or *lanoline*, is woolfat. The latter is softer, less irritant and more penetrating through the skin. It is more greasy and less irritating than vaseline. It is a better absorbent of water and keeps the surface dry. It is therefore used in superior types of cosmetics, as a base.

Adeps benzoinatus—3% has better keeping quality in the tropics than lard itself, which becomes rancid easily. *Saeuum* or *suet* is the sheep omental fat and has got similar properties as above.

Waxes and Soaps: (a) *Sapo animalis* is prepared with sodium stearate. (b) *Sapo duras* or castile's soap, is prepared with sodium oleate and (c) *Sapo molles*, is prepared with potassium oleate. *Linimentum saponis* has a strength of 8%.

Soap is a cleansing agent and because of its power of penetration, certain drugs are used in this vehicle *Internally*, it is an antacid and helps in the emulsification of fats. Hard soap is used in pharmacy, as basis for preparation of pills and plasters and soft soap for liniments.

PROTECTIVES AND ADSORBENTS

They comprise inert insoluble substances, meant for protecting the skin and mucous membrane against irritating agents and also for adsorbing exudations. The astringents are also endowed with these properties but they produce roughness and induration of tissues, which they come in contact with.

The protective *dusting powders* are—talc, ZnO, stearate, Mg. stearate, boric acid, starch, Bi subgallate and colophony. They all act as mechanical protectives and adsorbents for skin and mucous membrane of the G.I. tract. The important members are—bismuth, magnesium and aluminium salts, which have already been studied elsewhere. Activated charcoal also comes under this category and is used in dyspepsia and aerophagy. This also applies to kaolin and pectin, the last being obtained from citrous fruits and used in cases of diarrhoeas.

Starch: or *amylum*, is obtained from maize. It is a bland, non-irritating substance, forming the basic constituent for all dusting powders *Glycerinum amyli*: 8-5% is sometimes used for chilblains and barley water acts as a demulcent and diuretic.

Colophony: or resin of pine, is an adhesive, protective and skin stimulant. *Emplastrum colophony*, consisting of resin—10%, lead plaster—85% and hard soap—5%, acts as a soothing, adhesive plaster.

Pyroxylinum: It is the nitrocellulose of cotton wool and is highly inflammable. *Collodion-flexile* contains 2% of pyroxilin. When painted on the skin, it leaves behind a thin layer, which is impermeable to air and moisture and thus checks irritation. It may be applied on the abraded skin, nipples and also for arresting haemorrhages.

Dimethicines: a silicon oil, which is used as *dimethicine ointment* for supplying a non-wetting film on the skin, resistant to water-soluble substances but not to organic solvents and detergents.

IRRITANTS AND COUNTERIRRITANTS

The presence of 'referred pains' in certain diseases is an established phenomenon. For example: (a) shoulder pain in pneumonia, (b) arm

pain in angina pectoris (c) epigastric cutaneous pain in pylorospasm and (d) trigeminal neuralgia from various teeth.

The idea of counter irritation seems to have been borrowed from the above. The counterirritant acts by producing local irritation, leucocytosis, axon-reflex, release of histamine and relief of distal inflammations as shown in *Plate XLV: Fig. 117 (a) & (b)*.

The following are the agents used for this purpose: (a) mustard, (b) cantharis, (c) aconite, (d) belladonna, (e) camphor (f) methol (g) tincture iodine (h) turpentine and also (i) dry and wet cuppings.

Cantharis: The *spanish fly* or *Cantharis vesicatoria* contains the irritant principle, cantharidine. There are two official preparations—(a) *Emplastrum cantharis* (b) *Liquir epispasticus* or *blistering fluid*. The first produces blisters in 4-6 hrs. and the second in $\frac{1}{2}$ hour. They are to be applied on the skin after cleansing. The plaster should be removed after 6 hours, the blister incised and dressed with boric acid. Cantharis is not usually absorbed through skin and does not damage the true skin. It is, however, a marked G.I. and renal irritant with doubtful aphrodisiac and hair tonic properties, for which also, it still finds its traditional uses sometimes.

Mustard: *Sinapis nigra*, containing the pungent, volatile principle *allyl isothiocyanate*. The plaster produces rubefaction in 30, and blistering after a longer contact. The ulcer heals very slowly. Unlike contharides, it injures the dermis and penetrates into tissues, more readily.

Capsicum: *Tinct. capsici*—0.3-1 ml. and *Ung. capsici*—25%. It is a condiment with carminative and counterirritant action and is also used in *alopecia areata*, without much effect.

Bee Venon: It is sometimes used in rheumatism by intracutaneous injection. It contains histamine.

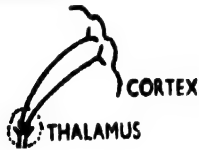
Cupplings: There are two types—the *dry* and the *wet* i.e. with or without scarification. In wet cupplings, aseptic bandaging is necessary. They produce local irritation, leucocytosis and have been used in acute bronchitis, sciatica and rheumatism. Their uses have almost been discarded now.

CAUSTICS AND ESCHOROTICS

Corrosives: On topical application, they destroy tissues and as most of them also produce scars, they are known as *eschorotics*, while some

Plate XLV

Higher centres are receiving impulses from two sites. Attention diverted from site of actual pain to the site of application of irritant. Intensity of pain related to organ is reduced.



Perception of pain from the hollow viscus here

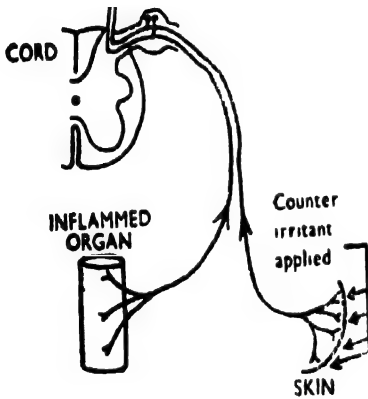
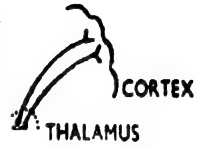


FIG. 117(a)

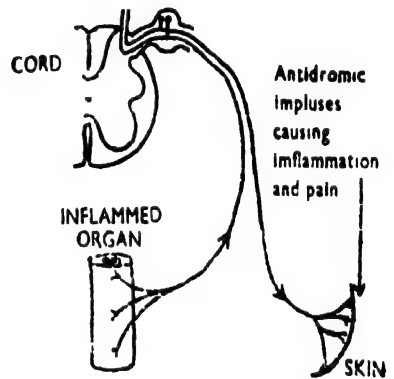


FIG. 117(b)

Mechanism of Action of Counterirritants

like alkalis, redissolve precipitated proteins and produce damages of tissues, thus acting as *caustics*.

Glacial acetic acid, trichloroacetic acid, exiccated alum, phenol, podophyllum resin, belong to these groups and are used for destroying warts, keratosis, hyperplastic tissues, fungal and eczematoid dermatitis. They are to be used with caution, avoiding accelerated proliferation of tissues after the stage of destruction is over.

Keratolytics: These are the desquamating agents like benzoic and salicylic acids, resorcinol and some of the thiols. They loosen the epidermis for desquamation and are used for *dermatophytosis* and *acneform* dermatitis.

ANTISEBORRHOEICS

A number of substances—benzoic and salicylic acids, sulphur and mercury compounds, are used for the management of certain scalp conditions. The important drugs for the treatment of *seborrhoea* are:

Selenium Sulphide: A bright-orange, insoluble powder, used for dandruff and seborrhoea. On local application, it is usually nontoxic but it is not so when the dust is inhaled in the form of selenium sulphide. **Selenium sulphide detergent suspension**—2.5% is used for shampooing of scalp, in certain cases. **Cadmium sulphide**—1% suspension, is also used for *seborrhoea capitis*, in the same manner.

MELANISING AND DEMELANISING AGENTS

Many drugs, in their toxic effect, involve the skin. Some of the aromatic compounds like PABA and hydroquinone and quinine effectively absorb U.V. rays and are used as 'sun-screens'. Others like chloroquine and mepacrine produce light sensitive eruptions, in susceptible persons.

Methoxsalen: or *xanthotoxin*, obtained from the Egyptian plant *ammi-magus*, contains *psoralens* and sensitises the skin to U.V. light, in 1 hour, lasting for 8 hours, when given orally. Topical application is more effective. It thickens the stratum corneum, produces mild inflammatory changes and pigmentation. It is used as 10 mg. capsules or tablets or 1% lotion, followed by a controlled exposure to sunlight. It is sometimes used in idiopathic vitiliago. If the melanocytes have been destroyed, it does not work.

Monobenzone: It is a hydroquinine derivative which is used in rubber industries and has 'amelanotic properties'. It is an antioxidant and interferes with the biosynthesis of melanin by blocking tyrosinase and thus preventing the conversion of tyrosine to dihydroxyphenyl alanine, the precursor of melanin. It takes weeks to show any effect. *Lotion*—5% and *ointment*—25%, are applied on hyperpigmented areas, 2-3 times/day, for 3-4 months and then 1-2 times/day. In hyperpigmentation of Addison's disease, pregnancy and generalised lentigo or severe forms of freckles, the drug is sometimes made use of.

II. NOXIOUS GASES AND VAPOURS

A number of noxious gases and vapours of industrial and other origin, pollute the atmosphere and produce deleterious effects on the health of the urban population. Some of these, which will be dealt with here, are—carbon monoxide, hydrocyanic acid, benzene, kerosene, carbon tetrachloride and organic solvents poisonings poisoning.

CARBON MONOXIDE

Its typical properties are only of toxic and no therapeutic value. Coal gas contains 10% and water gas, 30-40% of CO, and is used for illumination purposes. Stoves, furnaces and coal mine fires are the common sources for carbon monoxide.

Its toxicity is due to its ready combination with hæmoglobin, forming COHb and consequent hypoxia. The affinity of Hb for CO, is about 20 times more than for O₂. Reduced oxygenation leads to tissue toxicity, feeling of tightness, suffocation, mottled appearance, severe headache, syncope, coma, weak pulse and respiration. The heart is extremely sensitive to hypoxia and there are E.C.G. changes. *Chronic poisoning* occurs in tunnel workers and occupational labourers. It is excreted through lungs and O₂ and CO₂ facilitate its elimination.

Treatment comprises—fresh air, artificial respiration, O₂ therapy under two atmospheric pressure, exchange transfusion and methylene blue in small doses.

HYDROCYANIC ACID

It is one of the most rapidly acting poisons and certain countries use it now for the execution of criminals. Its toxic effect is due to the cyanide ion. Consequently, all the salts share, depending of course, on their degree of dissociation. Hydrocyanic acid is used in metallurgy,

electroplating, metal cleaning and as insecticide. It causes cytotoxic hypoxia by reacting with the trivalent iron of cytochrome oxidase, forming *cytochrome oxidase—CN* and also *cyanomethaemoglobin*. Thus cellular respiration is inhibited. It is converted to thiocyanate by the enzyme rhodanase. There is marked depression of CNS and also effects of hypoxia on the C. V. system.

Poisoning occurs from its suicidal or genocidal uses. The symptoms are—giddiness, cyanosis, unconsciousness, asphyxial convulsions and characteristic smell of bitter almonds, in the breath.

Treatment comprises immediate use of *sodium nitrite*—0.1—0.5 gm. in 10 ml. water, injected in 3-4 minutes. If time is an important factor, inhalation of *amylnitrite* is useful. This treatment is followed up by the use of sodium thiosulphate—12.5 gm/50 ml. which is to be repeated, if necessary.

According to Chen, under optimal conditions, the cure-rate could be as high as even 98%.

BENZOL

Present in petroleum, it is somewhat different from benzene, chemically and is used as solvent and paint remover. Poisoning effects are both *acute* and *chronic*, with CNS and G.I. troubles and also blood changes, leading to *aplastic anaemia*. Benzene is metabolised to polyphenols in the body and then conjugated. The *therapy* is preventive and symptomatic and blood transfusion is necessary.

GASONENE AND KEROSENE

The toxicity is due to the presence of naphthanic and aromatic hydrocarbons and comprises C.N.S. depression, chemical pneumonia, pulmonary oedema and also some euphoria and confusion. In some cases of ingestion, vomiting and diarrhoea are produced. *Emetics* are usually contraindicated and so also is lavage. Vegetable oils, supportives, as well as, O₂ therapy are advocated. Use of antibiotics and caffeine, is also recommended.

CARBON TETRACHLORIDE

A reactant solvent which is used as a fumigant for food grains and also a fire extinguisher. It is liver nephrotoxic and causes lower nephron nephrosis. Its toxicity may be acute and/or chronic. There is no specific treatment but O₂ inhalation and liver protectives, are used.

ORGANIC SOLVENTS

These are principally used in the preparation of liquours, thinners and enamel paints. They usually have pleasant odours and exhilarating actions. Children and juveniles have started using them in certain countries, for a *cheap kick*, particularly, when they have traits of delinquency and this is becoming a social danger in many advanced countries.

III. DIAGNOSTIC AGENTS

A number of substances are used for the detection of functional and organic disorders, in the body. They are:

- (a) Contrast media for roentgenographic studies
- (b) Use of dyes for functional tests of organs
- (c) Microbial proteins for diagnosis of diseases

Substances used for *contrast media* are usually pharmacologically inactive, as they are not absorbed. Similarly, the dyes are not metabolised, so that, their concentration is not modified. The proteins evoke sensitivity reaction, if the person has already been preinjected with them. From the positive response the diagnosis is made.

CONTRAST MEDIA

These are *radio-opaque* substances which permit the outlining of structures to be visualised from the shadows cast. Some of them are used for X-rays of the G.I. tract and others of the bronchial tree, fallopian tube, blood vessels and pyelography.

CLASSIFICATION

BARIUM COMPOUNDS IODINE COMPOUNDS

Barium sulphate.

Water Soluble: Sodium acetoxoate, diiodone, iodixyl, sodium diatrizoate, methiodal sodium, sodium iodomethamate, sodium iodipamide.

Water Insoluble: Propyliodone, ethyl iodophenylundecenoate, lipiodol, ippanoic acid.

HALOGENATED COMPOUNDS

Phenolphthalein and iodophthalene, pheniodolphenobutiodil.

BARIUM SALT

Though bismuth was discovered much earlier, BaSO_4 is mostly used for the radiography of the G.I. tract, in the form of *Ba meal* and *Ba enema*, in doses of 300 and 400 gm. respectively, in the form of suspensions of the fine powder in water.

It is heavy and tasteless and is sufficiently opaque. It is not absorbed from the G.I. tract but BaCl_2 is. Therefore, due precaution should be taken in the storage and dispensing of these salts. No error should be committed in using the salt as they are otherwise physically similar.

BaCl_2 is pharmacologically active and also very toxic for heart, G.I. tract and several other functions.

IODINE COMPOUNDS

Compounds in organic combination are used as contrast medium for the exploration of a number of hollow viscus. Some of them are soluble in water and others in poppy seed oil. The radio opacity is due to the organic molecule. They are used for visualising the arteries, brain tumour, blockage of the spinal cord. Due precaution about the sensitivity and intolerance of the patient, has to be taken.

Water Soluble Compounds: These are several, as detailed below:

Na acetrizoate (Urokin): It is the sodium salt of 3-acetylamine—2, 4 6-tri iodobenzoic acid. The iodine contents are 65.8% and 70%. A solution containing 46% of iodine, stabilised by ethylene diamine tetraacetic acid and sodium hydrogen phosphate, is also used for nephrography, retrograde pyelography and angiocardiology, by I.V. injections. *Toxic side effects* are—headache, nausea, feeling of warmth, itching, sneezing, thirst and weakness. The injection should be given slowly, inside the vein, as otherwise, inflammatory reactions may occur.

Diodone (Diodrast): A diethanolamine derivative containing 50% of iodine. A 35% solution, containing 17.5% of iodine and also 50% solution, are used. The drug is not metabolised in the body and quickly excreted in urine. It is therefore used for urography or excretion pyelography, by the I.V. route. A viscous solution is used for hystero-salpingography. The side-effects are the same as above.

IodoxyI (Pyelectan): containing 50-52% iodine, is used for the same purpose. It is a vasodilator and imparts a sensation of warmth, flushes and thirst. After injection, painful venospasm and thrombosis may occur. It is excreted in urine unchanged and is used for excretion pyelography.

Na diatrizoate (hypaque, cardiograffin): It is similar in nature and is also used for the same purpose. A special oral preparation for contrast G.I. tract radiography is also available.

Methiodal sodium (skiodan Na) and **Na iodomethamate**: are some of the other preparations used in urography work.

Water Insoluble Compounds: The following two preparations are mostly used:

Propyliodone (diomosil): It is related to diodone and is used as a 50% suspension or 60% solution, in arachis oil. It is used for *bronchography*. As its elimination is slow, a series of skiagrams can be taken to show the filling up of the alveoli.

Ethyl iodophenylundecanoate (myodil): This contains 30% iodine and is used for *myelography* as a substitute for lipiodol. The iodised ethyl ester in poppy seed oil containing 40% of I in organic combination and also 10% and 40% viscous solutions, are available. Their absorption and elimination are slow. A chlorinated and iodinated groundnut oil, is marketed for use.

ORAL CHOLECYSTOGRAPHIC MEDIA

These, after ingestion or injection, are excreted in bile, thus allowing the visualisation of the biliary tract.

Halogenated derivatives of *phenolphthalein*, including tetrachlor and tetrabromo derivatives, were previously used but they have now been replaced by *tetra iodophenolphthalein*. Special preparation of patient with fatty diet, is necessary for getting better skiagrams.

Iodophthalen (opacol) or **Na tetraiodophenolphthalen**: Os/inj; pheniodol (*priodax*), as granules or tablets, containing 51% of iodine; phenobutiodil (*biliodyl*), lopanoic acid (*telepaque*), containing 66% of 1-3 gm. doses; Na ipodate (*oragraffin*), a new oral cholecystographic agent is available as Na and Ca salt. *Dose*: 3-6 gm/os and Na iodipamide (*cholograffin*), a water soluble compound, used in a dose of 40 ml. of 20% solution, I.V., for visualising intrahepatic ducts. A modified preparation of methyl glucamine of Na iodipamid, is used for hystero-salpingography.

VENTRICULOGRAPHY

This is a method for the localisation of brain tumours. A needle is introduced into the ventricle on the one side, C.S.F. is drawn out,

sterilised air introduced and skiagram taken. From the distortion of the shape of the ventricle, diagnosis of tumour is made. If the tumour is centrally located, the Foramen of Monro, which allows air to pass from one ventricle to another, is blocked. The air thus introduced gets absorbed in a few days.

CLINICAL USES

Alimentary tract	Barium sulphate, sodium diatrizoate (<i>gastrograffin</i>)
Cholecystography	Ipanoic acid (<i>telepaque</i>), ipodate sodium (<i>oragraffin</i>), iodipamide sodium (<i>cholograffin</i>)
Urography	Diatrizoate sodium (<i>renograffin</i>), acetrizoate sodium (<i>urokan</i>), iothalamate (<i>conray</i>)
Bronchography	Propyl iodine (<i>dionosil</i>)
Angiography and angiocardiology	Diatrizoate sodium (<i>cardiograffin</i>), iodopyracet (<i>diodrast</i>), iothalamate (<i>conray</i>).
Myelography	Iophendylate (<i>pantopaque</i>)
Hystero-salpinography	Iodized oil (<i>lipiodol</i>)

ENCEPHALOGRAPHY

In this case, filtered air is injected through a lumbar puncture needle. The air passes into the ventricles and the commissures of the brain. By stereoscopic skiagrams, if any inequality of air shadow is found, diagnosis of intraventricular tumour and blocking of the foramina, is made out.

DIAGNOSTIC TESTS

These are carried out with several drugs, bacterial toxins and also selected dyes. The following drugs are the important ones:

- (a) *Neostigmine test*: for the diagnosis of *myasthenia gravis*.
- (b) *Histamine test*: for the diagnosis of *true achlorhydria*.
- (c) *Adrenergic blocking agents*: pentolamine, benodanil and priscocholine for the diagnosis of pheochromocytoma.
- (d) *Metopirone and amphenone*: used for the diagnosis of diseases of the anterior pituitary gland, due to the inability of the gland to secrete normal amount of hormones.
- (e) *Fluoresceine test*: is also used for the diagnosis of corneal ulcer.

Proteins: (a) *Shick's test* used for diphtheria
 (b) *Dick's test* for scarlet fever

- (c) *Frel's antigen* for soft chancre
- (d) *Tuberculine test* for T.B. and
- (e) *Cassoni's test* for the diagnosis of hydatid cyst.

All these tests have been detailed in their respective chapters.

FUNCTIONAL TESTS

A number of substances permit the assessment of circulatory and metabolic functions from their distribution and excretion in the body.

Evans Blue: or T 1824, was discovered in 1920, for estimation of *blood volume* and later, for *cardiac output* and arterio-venous shunt. It does not diffuse much into tissues and can be chemically estimated. Its toxicity is not very high. It may give slate blue discoloration, if used repeatedly. It is a greenish blue powder, soluble and dispensed as 0.5% solution in 5 ml. ampules. Tagged Cr_{51} and P_{32} are also used for this purpose.

Indocyanine Green: It is now more used for the measurement of cardiac output by the indicator dilution method and also for determining the hepatic blood flow and hepatic functions. It is available as dry, sterile powder in 25 and 50 mg. vials, from which, 5 mg. is made into solution for injection.

Sulphobromophthalein: Introduced in 1924 and 1945 for the evaluation of liver function and hepatic blood flow. The dye is rapidly cleared from the circulation to liver, in the absence of any hepatic disease. **Dose:** 2-5 mg/kg. I.V. Its concentration in serum is determined at 5 and 45 mins. interval. The percentage of the dye retained in 45 mins. is elevated in liver diseases. For estimating blood flow, catheterisation of arterial and hepatic veins, is necessary.

Inulin and P-amino hippurate: 10-20% solutions, are jointly used for studying the renal functions. Continuous I.V. infusion and timed urinary collection and estimation are necessary. The rate of clearance/minute is to be determined. *Creatinine*, *mannitol*, *urea* and *di-iodotrast* are also used for this purpose. **Toxicity**—usually negligible but PAH may sometimes give convulsions.

IV. ACCESSORY THERAPEUTIC AIDS

There are still two other groups of agents, which though not drugs in the truest sense, are often used in accessory therapeutics. These are (a) *Hydrotherapy* and (b) *Physiotherapy*.

The basic principles involved in these forms of therapy are the following:

HYDROTHERAPY

The spring waters act by virtue of their (a) chemical composition, (b) thermality and (c) oligo-dynamic effect of trace elements. They have all been studied chemically, experimentally and clinically, under controlled conditions. These waters are used *orally*, in the form of *baths, douches* and *mud baths*, in various diseases. The SPAS are very well developed in France, Germany, Czechoslovakia and many other European countries. Besides the benefit of treatment, they also offer congenial environment, climatic salubrity and entertainment, as a good change, for these patients.

IMPORTANT SPAS

Vichy waters contain Na, K, Ca bicarbonates, Mg, Mn, Fe and CO_2 and also radioactivity and are used for tropical, alcoholic and post malarial livers and also as cholagogues.

Plombier and Chatel-Guyon waters: These are used in cases of chronic constipation, ptosis, colitis, cholecystitis and dyspepsia.

Mont Dore and La Bourboule waters, containing As, CO_2 , NaHCO_3 , $=\text{NaHCO}_3$, NaCl and Ca silicate, are used in cases of pulmonary diseases.

Royat-Bagneole de L'Orne and Orizsa Waters: containing carbonates, sulphates, Fe and CO_2 are used in C.V. diseases, secondary anaemias and various types of ulcers.

Luxeuil Water: This is used for vaginal irritation in cases of dysmenorrhoea, salpingitis metritis, amenorrhoea and sterility.

Uriage and Cauteret Waters: are good for E.N.T. diseases.

Vittel and Evian Waters: act as diuretics in renal diseases.

Dax Water and Mud: Containing Ca and Mg. sulphates, radioactivity and thermality, are used for chronic rheumatism.

In this subcontinent, a few thermal stations have also been existing in Bihar, Sind and other areas. These are *Philipkund*, *Surajkund* and *Mangopir*, which resemble Vichy, Evian and Uriage types of stations, respectively, referred above. The last has long been used for *leprosy* patients as well.

PHYSIOTHERAPY

It refers to the treatment of diseases by physical agents of light,

electricity and radiations and comprises (a) U. V. and I. R. therapy, (b) Diathermy (c) Deep X-ray, radium and cobalt beam therapies.

Diathermy: In this, high frequency current is passed through body tissues and the resistance offered by the latter to the former, generates graded doses of bilateral heat, for relief of inflammatory conditions. It is of particular value in cases of osteoarthritis, fibrositis, sinusitis and endometritis. *Diathermy cautery* is used for electrocoagulation with minimum blood loss from the incised tissues.

In *short wave therapy*, the body is placed in an intense field of short electro-magnetic waves and the tissues underlying the skin can thus be subjected to heat therapy. Its indications and uses are the same as above.

Ultra Violet Light: Either *mercury vapour* or *carbon arc* lamp, is used. The light causes tanning effect on the skin with production of ergosterol, thus increasing body resistance against diseases.

Uses: (a) improvement of general health (b) rickets (c) tuberculosis. It is also useful in case of chronic eczema, fungal infections and leucoderma. *Infrared therapy*, which has a more limited field of action, is good for the relief of neuralgic and myalgic pains.

Deep X-ray, Cobalt Beam and Radium Therapies: These are used for the treatment of malignant tumours. They act on the proliferating cells and due to their ionising effects, the cells undergo necrosis and also the blood vessels. *Deep X-ray therapy* is given up to 250-400 Kv. but has the disadvantage of skin reactions, while in the case of *cobalt beam*, the rays are of shorter wave lengths and more particularly, than X-rays and are not therefore, absorbed by the skin. Consequently, higher cancericidal doses can be given without any skin reaction.

In the case of *radium*, the same advantages as of *cobalt beam* are present, as the rays are of very short wave length. *Radium needles* can be infiltrated into the tumour tissues for giving the maximum dose without affecting the neighbouring healthy tissues of the cartilages or bones. If the *radium bomb* is used, one can have intensified exposure in small areas for a short time. *Cobalt needles* act on the same principle as radium needles but are less expensive and also less penetrating. Their *penetrating effect* is up to 400kv. Their *indications* are: malignant tumours of all kinds—epithelioma, rodent ulcer, leukaemia, testicular or ovarian tumours and Ewing's tumour. *Deep X-ray therapy* is used for osteo-arthritis and endometritis.

INDIGENOUS MEDICINAL PLANTS

Use of medicinal plants, growing in India, has come from the days of Ayurvedic and Unani medicines and even earlier. Comprehensive informations, in respect of these drugs, are available in

Watt's-Dictionary of Economic Products

Dymock's—Pharmacographia Indicus

Kirtikar and Basu's—Atlas of Medicinal Plants

Chopra's—Indigenous Medicinal Plants and Poisonous Plants of India

as well as, from a large number of current literature and published papers, including review articles, written by several workers, during the recent years.

If one goes through these compilations, one is bewildered by the impact of conflicting trends of thoughts which cannot easily be avoided in any old empirical science. However, as use of these drugs has come through successive generations and vegetable drugs have been the forerunner of modern medicines, it may be advisable to briefly go through some of the salient features of these drugs, as known today, and leave the rest for further studies, which are going on in this country, at present, with great hopes for newer discoveries from this ancient field of medicine.

ACTION-WISE CATEGORISATION OF PLANTS

- | | |
|---|--|
| C.N.S.— <i>R. serpentina</i> , <i>A. calamus</i> , <i>N. jatamansi</i> , <i>H. monniera</i> , <i>Cellustrus</i> , <i>Cannabis</i> , <i>Datura</i> . | Bitters— <i>Kalmegh</i> , <i>Aristolochia</i> , <i>Tinospora</i> . |
| A.N.S.— <i>R. canescens</i> , <i>Hyatin</i> . | Ecbolics and Uterine Sedatives— <i>Ashoka</i> , <i>Hydrastis</i> , <i>Valeriana</i> . |
| C.V.S.— <i>Thebetia neriifolia</i> , <i>Alangium</i> , <i>T. arjuna</i> , <i>A. calamus</i> , <i>N. jatamansi</i> , <i>Vinca rosea</i> , <i>Alstonia</i> , <i>Callophyllum</i> , <i>U. indica</i> . | Haemostatics— <i>Ayapana</i> , <i>Calendula</i> . |
| Respiratory— <i>S. lappa</i> , <i>A. calamus</i> , <i>Adhatoda-vasaca</i> , <i>Achymanthus aspera</i> , <i>Cuscuta reflexa</i> . | Antiperiodic— <i>Berberis</i> , <i>Alastonia</i> , <i>Picrorrhiza</i> , <i>Tinospora</i> . |
| G.I.T.— <i>Euphorbia</i> , <i>Sida caprinifolia</i> , <i>Cassia</i> , <i>Cuscuta</i> , <i>Alangium</i> , <i>Daemia extensa</i> . | Antidiabetic— <i>Pterocarpus marsupium</i> , <i>Gymnema sylvestre</i> , <i>Coccinia</i> , <i>Shilajit</i> , <i>Eugenia jambolana</i> . |
| Anthelmintic— <i>Carica papaya</i> , <i>Cucurbita</i> , <i>Arnebia nobilis</i> , <i>Butea frondosa</i> , <i>Embellia</i> , <i>Veronica</i> . | Antiarthritis— <i>Asperagus</i> , <i>Vandarox</i> , <i>Dalbergia</i> , <i>Alangium</i> , <i>Sida humilis</i> , <i>Pacderia</i> , <i>Glycyrrhiza</i> . |
| | Anti-Infective— <i>P. corylifolia</i> , <i>Parmelia</i> , <i>Daucus carota</i> , <i>A. aspera</i> , <i>Berberine</i> , <i>Banakadali</i> , <i>Ocinum</i> . |

Diuretics — <i>Berginea</i> , <i>Carium</i> , <i>Borehaavia</i>	Volatile Oils — <i>Betel</i> , <i>Cuminum</i> , <i>Oleum</i>
<i>Cassia</i> , <i>M. azadirachta</i> , <i>T. terrestris</i> ,	<i>cassiae</i> , <i>O. pudina</i> , <i>O. ajowani</i> , <i>Psora-</i>
<i>Viola odoranta</i> .	<i>lium</i> , <i>O. sinapis</i> .
Purgatives — <i>Terpethum</i> , <i>Kaladana</i> , <i>Bel-</i>	Antifertility — <i>Butea</i> , <i>Lithosperm</i> , <i>J. curcas</i> ,
<i>ae-fructus</i> , <i>Jatropha curcus</i> , <i>Aloc.</i>	<i>Permelia</i> , <i>Pisum sativum</i> , <i>Dioscorea</i> ,
	<i>Polygonum</i> .
Astringents — <i>Myrobolan</i> , <i>Kurchi</i> .	Anticancer — <i>Polygonum recumbens</i> , <i>Sola-</i>
Demulcents — <i>Isapguhil</i> , <i>Agropyrum</i> .	<i>line</i> , <i>Vinca rosea</i> , <i>Heliotropium indica</i> ,
	<i>Cissus repens</i> , <i>Podophyllum</i> .

Of all the fields, so far explored, drugs acting on the *C.N.S.* seem to deserve some consideration. Consistent works on *R. serpentina* (Chopra, Mukerji, Bose & Kohali); *Herpestis monniera* (Malhotra and Das); *Cannabis indica* (Mukerji, Bose *et al*), *Cellestrus paniculatus* (Sheth); *Convolvulus pleuricaulis* (Berar); *Arboricine* (Chakravarti and Pal); are indicative of their sedative and tranquillising effects. *Herpestis monniera* and *hersaponin*, isolated from it, have been found to be endowed with sedative, analgesic and hypothermic activity. A related plant, *Withania somnifera* has shown potent ganglion blocking action. *Ashwagandha* seems to be modifying brain Ach level and *Cellestrus paniculatus*, the spontaneous motor activity and O_2 consumption, in mice. Similarly, *Sesile sibiricum* (Jamwel) and *Acorus calamus* (Dandiya) and the isolated active principles of *alpha* and *beta asorones*, seem to have demonstrative sedative and hypotensive action, with a quick component like chlorpromazine and yet lasting for 24 hours like reserpine. The quaternary salt of *hyatine*, an alkaloid of *Cessampelos pariera*, has shown neuromuscular blocking action (Pradhan, De and Ray) and some of its derivatives, C. V. and respiratory analeptic and convulsant actions, in experimented animals.

Amongst the other *C.N.S.* active plants, *myristica*, containing 2% of volatile oils, *Datura alba* containing appreciable quantities of alkaloids as atropine and hyoscine, *Valeriane officinalis* and *Vinca rosea* have shown varying degrees of sedative and hypnoctic actions with behavioural changes and also changes in Ach and 5-HT contents in brain.

Amongst the group of *cyanogenic drugs*, *cannabis indica*, has probably been the most studied from the standpoint of its physiochemical and psychological effects and addiction liabilities. The *cannabis resin* possesses a dual component of excitatory and inhibitory action of central and peripheral nature, with facilitatory effect on 'hexobarbital sleeping time', prolongation of reserpine and antagonism with 5-HT effects. It sensitises sympathetically innervated structures to catecholanines, which is preferential for noradrenaline to adrenaline. Charas also has

a central hypotensive effect and similarity with imipramine in some of its action. It is thus a complex drug deserving careful studies, as a physiological and biochemical tool, for elucidation of C.N.S. functions.

Amongst the *cardiovascular drugs*, *peruvoside* obtained from *Thevetia neriifolia* (Kohli, and Vohna) has shown digitalis like effect with a quick component of onset, good oral absorbability and reasonable duration of action. Similarly, 'jatamansone' from *N. jatamansi* and colophylloine a complex 5-phenylcaumarine from *calo-phyllum inophyllum*, have been found to possess antiarrhythmic activity (Arora *et al*).

The hypotensive action of *Rauwolfia canescens* has been studied by Das *et al*, and the alkaloid—'rauwolefine' assigned a central role in its vasodepressor effect (Tangri and Bhargava). Its adrenergic blocking activity has been found by Kohli, which is claimed to be more potent than even priscoline. Two alkaloids, ashwagandhine and ashwagandhinine, were obtained from the roots of *Withania ashwagandha* by Das *et al*, the former being more cardiogenic than the latter. Bose *et al*, 1961 separated out two different fractions, 'A' and 'B', from the alcoholic extract of *Jatropha curcas*, which showed antagonism to each other on blood coagulation and prothrombin bleeding time. The hypotensive property of alkaloids of *Alangium lamarckii* and *Alstonia scholaris*, has also been reported from the Institute of Biochemistry and the School of Tropical Medicine, Calcutta.

With regards, however, to the cardiovascular actions of indigenous drugs, it may be remarked that the majority of them show an initial depression, followed by stimulation, with very little chronotropic action. They are sometimes blocked by agropine and at other times, not. The effect is dose-dependent and may even be of toxic nature, because of the crude extracts, used. Unless, any of them, prove to be comparable to digitalis, in every respect, they are unlikely to be of much value in therapeutics. The problem cannot be solved till detailed studies with purified principles and clinical assessment, have been carefully made. Our own work on 9 reputed plants of the series of *T. arjuna*, *C. odolla Vincarosea*, *Tapioca* and finally a new variety of *Urginea*, has not been able to establish a drug superior to digitalis in any appreciable manner.

Amongst the *bronchial antispasmodics* and expectorants of Ayurvedic fame, a special reference is made of *Adhatoda vasica* and its active principle *Vasicine*, present in leaves and roots. The tincture and syrup (2-4 and 4-8 ml, respectively), are commonly used in expectorant cough mixtures. Similarly, *Achorus calamus* and *Saus-suria lappa* also find their uses as bronchial antispasmodics and expectorants.

torants, mostly in the form of liquid extract. Their antispasmodic action, however, is poor and only about 1/50 of ephedrine.

G.I.T.: Of all the important systems of the body, excepting C.N.S., Ayurvedic medicine has proclaimed to be a rich lore of G.I.T. drugs, consisting of bitter stomachics, carminatives, laxatives and purgatives.

Amongst the *laxatives* and *purgatives*, the place of *aegle marmelos* or *Bela-efructus*,—containing marmelodin, pectin, tannin and mucilage, has been emphasised. The extract—4-8 ml and decoction—15-60 ml, have been popularly used in spastic-constipation, while, the baked unripe fruit, in dysentery and sprue. Its root bark also finds a place in *dashamula*, used empirically, as febrifuge. Similarly *Isaphguhla* or *Plantago ovata* seeds, are extensively used as mild laxative in spastic colitis and chronic constipation, as it is mild and non-irritant. Another plant—*Agropyrum* or *couchgrass*: decoction—15-60 ml and Liq. extract 4-8 ml, is believed to be a soothing demulcent for G.I. and urinary tracts. Amongst the *purgatives*, *Ipoemia turpetheum* and *kaladana*—2-3 gm, possess strong, drastic, irritating actions and are therefore seldom recommended for any routine use. *Other drugs* like *Alstonia*, *Picrorrhiza* and *Tinospora*—are sometimes used as bitter stomachics and antiperiodic. *Myrobolan* or *heritaki*—3-4 gm, is an important astringent and widely used in indigenous medicine; also *Kulnegrh* or *andrographis* and its extract—1/2—1 ml is used as bitter liver tonic.

Some of these and other plants have been studied in recent years for their GIT action—*Eupporbia dracunculoides*, *Daemia extensa* (Prasad and Chakravarti) for spasmogenic action; *Cissia javanica*, *Alangium lamareckii* and *Cocculus hirsutus* (Khorana, Sanyal, Das Gupta and Dass) as laxative *Sida caprinilia* (Prasad and Achari)—acetylcholine like action and *Cuscuta reflexa* (Prasad)—carminative effect.

There is scope for a more detailed study in this field, as some of them may have a place in gastric-intestinal disorders, as carminative and laxative. But here again, the evaluation has to be carefully done and the problem pursued by clinical studies, before any definite opinion on their actual value, could be forwarded.

Volatile oils: There are several of them with their usual carminative and other properties. *Betel* or *pan*, extensively used in India, has an alkaloid, and phenol, besides its pungent, aromatic oil. It is a gentle sialogogue, stomachic and carminative and also used locally in hepatitis, bronchitis and ear-ache. *Oil. ajwan*—is obtained from *Carum capticum*. *Aqua ptychotis* is used is a *gripe cure* in infants, as a domestic medicine. *Cuminum* (IPL) or *jira* oil and *Jalghira* contain cumic

aldehyde, comparable to thymol, and used as a relishing appearative and carminative, in hot seasons, before a dinner. *Ol. cassiae* gives aqua and spirit preparations: 1/2—1 ml. having the same type of action as cinnamon. *Pleum pudinae* (IPL)—Spirit—1/2—1 ml. resemble peppermint and acts as a carminative and flavouring agent. Finally, *Psoralea corylifolia* or *Babchi* oil, containing *psoralen*, is used in vitilago as a melanising agent, mentioned earlier.

We had, at one time, given a lot of importance on indigenous *Anthelmintic drugs* and several of them—*Carica papaya* (Bose *et al*, Dhar *et al*), *Arnebia nobilis* (Patel and Patel), *Sphaeranthus indicus* (Gupta *et al*), *Psoralea corylifolia* (Gandhi *et al*) and *Cucurbita maxima* (Shrivastava and Singh), had been preliminarily investigated. One has to be very critical about the value of indigenous anthelmintic drugs, in view of highly potent, synthetic, broad spectrum anthelmintics, already in our possession.

Much has been said about potent *diuretics* in Ayurvedic medicine. More than a dozen of reputed plants have already been studied at different centres, from the times of Col. Chopra, Caius and Nadkarni. In recent years, Gujral, Bose and Bhide have studied several of them and Gujral has categorised them as of *good*, *'moderate* and *'mild* action. In the first category, the names of *Boerhaavia diffusa*, *Viola odorata*, *Cassia occidentalis* have been included. Our experience with those which we had studied in our laboratory, has not been very encouraging. Essential oil bearing plants could have some diuretic action but that type of effect could not be of much value in cardiac, hepatic and renal oedemas.

At one time, we had also great expectation from *Indigenous Anti-diabetic Drugs*, because of their reputation in Ayurvedic literature. Several centres like Poona, C.D.R.I., Indore and Cuttack, had been engaged in this work. The studies on *Casaria-esculenta* (Gupta and Nautiyal); *Pterocarpus marsupium* (Trivedi, Harnath, Gupta & Shah); *Ficus bengalensis* and *F. glomerata* (Aiman and Joglekar); *Gymnema sylvestre* (Deshmukh); *Momordica charantia* (Gupta, Sharma, Kulkarni and Gaitonde, Chatterjee); *Shilajit*—(Chopra and Gupta); *Allium sepa*, *Lochnera rosea*, *Rivea cuneata* (Govinda Rao); *Bolichos lab-lab*, *Phasolos munja* (Shrinivasan) have not shown very convincing results. Recently, Madhok and Rao reported on the hypoglycaemic effect of the steroid containing *Adhatoda vasaca*, for about 2 hours. From an analysis of all these works, it appears that while a number of workers consider their actions as weak and undecisive, several others are enthusiastic even about the action of *Momordica charantia* (Karela) in diabetes. In the field of science, one has to be very critical about an

observation and accept a definite negative action as important as a positive one, irrespective of what our old literature proclaims about it. This is one of the dangers of working on old drugs of reputation.

A lot of work has also been carried out on *Anti-inflammatory* and *Anti-arthritis* actions of indigenous drugs in recent years, by using the usual non-specific techniques of producing inflammatory reactions in laboratory animals. The work of Gujral, Sharma and Madan on *Balsamodendron mukul* (Guguhl) and *Glycyrrhiza glabra* (Mulethi) showed good anti-inflammatory and anti-arthritis properties, comparable to *hydrocortisone* and *phenylbutazone*. The active principle of *Glycyrrhiza glabra* was found to be 'glycyrrhizine' and drugs like *Asparagus racemosus*, *Sida humilis*, *Vanda roxbarghii*, *Paederia—foetide*, were also studied by Tripathi, Prasad and Singh, in recent years. Similarly, *Melia azadirachta* has also been found to possess anti-inflammatory action (Sankara Narayanan and Sirsi). All these works are still inconclusive and are unlikely to take the place of any of those already used.

Of late, a number of workers have been engaged in studying the *antiinfective* action of indigenous drugs: *Psoralea corylifolia* (Gaind), *Daucus carota* (Bhargava), *Thespesia populnea* (Gaind and Bapena), *Piper betel* (Banger), *Cassia occidentalis* (Gaind), *Asterocantha longifolia* (Parashar and Singh), *Parmelia spp.* (Culberson), *Andrachne aspera* (Devasari and Khosla), *Berberine* (Dutta and Pakrashi) and unripe-*bankadali* (Dutta). This is a very treacherous soil, in which, study with purified principles and standard chemotherapeutic techniques, by *in vitro* and *in vivo* methods, as well as, careful clinical evaluation, are warranted.

The discovery of *Antifertility* agents from vegetable sources had evoked considerable interest in this field, in our workers and the government specially, after the discovery of oral contraceptives from Yam. Sanyal, observed *Pisum sativum* to have antifertility action, which could not be substantiated by other workers and 50% of female rats, under investigation, became pregnant (Thiersch, 1956).

Several other plants—*Jatropha curcas*, *Butea frondosa*, *Polygonum hydroppiper*, *Lithospermum ruderalis*, *Mallotus philippinensis*, *Calotropis gigantea* have been studied by Gujral, Shah, Zadina, Khanna, Varma, Chaudhari, Parasar, Granston, Plunket, Nobel and Grant, mostly from 1960 onwards and their antifertility action assigned to a large series of mechanisms—antichorionic gonadotrophin, anti-implantation, or antioestrogenic action, accompanied by atresia of ovaries, uterus, etc. Most of these works seem to have been carried out rather hurriedly, forgetting the golden rule of establishing the action first before

trying to explore and explain their mechanisms of action. This may be one of the reasons why we discover drugs more often than reject and do not continue our work on one problem, long enough to bring it to a conclusion.

The same remark may be applicable to our Indigenous *Anticancer* drug work, from several centres in the country, including Cancer Institutes, on *Polygonum recumbens*, *Vinca rosea*, *Heliotropicum indicum*, *Podophyllum hexandrum* and many others. One will still have to wait for finding out their actual status which would not be possible till their active principles and chemical structures are known and the techniques of experimental carcinogenesis and tissue culture, very accurately established.

Dr. Udupa and Prasad from 1964 onward, have been studying the effect of medicinal plants like *Cissus quadrangularis* on fracture healing by modification of mineral metabolism. This is also a difficult terrain needing critical assessment, for drawing any definite conclusion.

Conclusion: The above account, though incomplete and inconclusive, gives an idea about the actual and prospective fields of study. Much of the work of recent years has been carried out with newly acquired techniques and motivation for newer discoveries. That *per se*, might have been a limitation for highly fruitful work, which needs correct organisation and approach. As these have been lacking, the outcome has not been fully encouraging.

Indigenous drug research, while still occupying a place in our overall drug research in the country, has to be carried out very differently from modern drugs, following the tracks of early pioneers, primarily concerned with a positive or negative finding first, influenced by no other consideration but accuracy of observation and simple, logical conclusions.

If this is done, it is not unlikely that something new will come out of this work provided that the list of the plants is carefully and very critically redrawn and the work carried out with a blank mind, weeding out redundant literature and applying the mind with dedication for research, divorced from inordinate urge for publications. The work has to be in much greater depth than at present, as some of the recent works in other laboratories, have been able to bring out what we had missed in respect of the active fraction in *Vasaka*, related to the fluidification of tenacious sputum or in our *Rauwolfia* work, in the thirties and forties of the century. Facilities and urges should enable us to work in depth, with a more critical mind than at present.

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APPENDIX

FORENSIC PHARMACY, SELECTED PRESCRIPTIONS AND QUESTIONS

FORENSIC PHARMACY

Forensic Pharmacy deals with the laws regulating the practice of Pharmacy. The following Acts and Rules are in force, at present:

Opium Act of 1878: Regulating the cultivation of poppy; Also possession, transport and sale of opium (including preparations containing more than 0.2% morphine).

Poisons Act of 1919: Regulating import, possession and sale of poisons, as given in Schedule E of Drug and Cosmetic Rules.

Dangerous Drugs Act of 1930 and Rules of 1957: They regulate the international traffic in all the drugs covered by the Geneva Dangerous Drugs Convention of 1925 and also the regulation of the manufacture of and internal traffic of, certain specified drugs such as cocaine, morphine, hemp and other narcotics.

Drug and Cosmetic Act of 1940 and Rules of 1945: Regulating the import, manufacture distribution and sale of drugs and cosmetics.

Pharmacy Act of 1948: Regulating the profession and practice of Pharmacy.

Drug Control Act of 1950 : For the control of sale, supply and distribution of drugs.

Drugs and Magic Remedies (Objectionable Advertisements) Act—1954: Intended for the control of advertisement of magic remedies and spurious drugs for diseases like cancer, diabetes, deafness etc. as scheduled in Drugs and Cosmetics Rules.

Medicinal and Toilet Preparations Act of 1955 and Rules of 1956: Providing for the levy and collection of duties of excise on medicinal and toilet preparations, containing alcohol, opium, Indian hemp and other narcotic drugs.

As per Drugs Rules of 1945, the supply of any drug as a prescription shall be recorded at the time of supply, in the Prescription Register. In Schedules C and C₁ of the Rules, is given a list of sera, vaccines, antibiotics, vitamins, hormones, digitalis, ergot preparations. In schedule E of the Rules, is given a list of poisons and their permissible strengths which are required to be labelled as Poisons, when dispensed, on the prescription of a registered medical practitioner.

Substances specified in Schedules H and L, such as barbiturates, sulphonamides, ACTH, antibiotics, PAS etc., can be sold in retail only in accordance with the prescription of a registered medical practitioner. The prescription shall be in writing and signed by the person giving it with his usual signature, name and address of the person for whose treatment it is given, indicating also the total amount of the medicine to be supplied and the dose to be taken.

Forensic Pharmacy thus, through the various acts and regulations, control and regulate the legitimate use of toxic and habit forming drugs for patients only and not for any other purpose.

SELECTED PRESCRIPTION

1. *Headache**A.P.C. Powder*

R/ Aspirin	0.33 gm.
Phenacetin	0.13 gm.
Caffeine	0.13 gm.

Fiat. pulv. Send 4 such powders.

Signa—one powder, as and when necessary.

2. *Migraine**Acute attack:*

R/ Ergotamine tartrate	1 mg. tab.
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Signa—keep two tabs under tongue when in pain, and repeat after one hour, if necessary.

3. *Acute rheumatic fever*

R/ Sod. salicylate	1.33
Soda Bi carb	0.66
Spt. ammon aromat	1.00
Tinct. Card Co.	1.33
Aqua ad.	30.00

Mft. Mist. Send 12 such doses.

Signa—one dose, six times a day after meals.
Vit. K (Menaphthone) 30 mg. tab. T.D.S. in prolonged therapy.

Vit. C-200 mg. tab. b.d.

Penicillin-125 mg. tab. b.d., orally,

Prednisolone—5 mg. tab/hr. till temp. normal.

4. *Gout*

(a) R/ Irgapyrine	300 mg.
Signa—one tab., 4 times a day or	
Inj. A.C.T.H.	200 units I.M.
or	
Cortisone	50 mg. tab.
Signa—one tab. q.d.s.	

(b) R/ Tinct. colchicum	1.33
Sod. salicylate	1.00
Soda bicarb	0.66
Aqua mentha pip ad.	30.00

Mft. Mist. Send 4 such doses.

Signa—one dose, q.d.s. after meals.

5. *Epilepsy**Grandmal:*

R/ Dilantin sod.	100 mg.
Phenobarbitone	30 mg.

Fiat. pulv.

Signa—one dose b.d.s. or more, depending upon the response.

Petitmal:

R/ Tridione	0.3
Signa—one cap. t.d.s.	

Psychomotor:

R/ Diamox 250 mg.
 Signa—one tab t.d.s.

For the treatment of epilepsy, to start in every case with a smaller dose, gradually increasing the same till the seizures are controlled and thereafter to put the patient on maintenance dose.

6. *Insomnia**In children:*

R/ Chloral hydrate 0.13
 Syrup orange ad 4.00
 Mft. draught.
 Signa—to be taken at bed time.

In adults:

R/ Phenobarbitone sod. 0.13
 Pot. bromide 0.33
 Syrup orange 4.00
 Aqua ad. 30.00
 Mft. Mist.
 Signa—one dose, to be taken at bed time.

For old people:

R/ Clutethemide 0.5
 One tab., to be taken at bed time.
 To be avoided in pregnant women.

7. *Congestive heart failure with hypertension*

- (a) R/ Digoxin 0.25 mg.
 Signa—2 tabs. stat, then 1 t.d.s.
 Subsequent doses to be guided by pulse.
- (b) R/ Ammon chlor 0.66
 Signa—one cap. $\frac{1}{2}$ hourly. 3 doses followed by inj. neptal 2 cc. I.M. twice a week.
- (c) R/ Chlorthiazide 500 mg.
 Signa—one tab. b.d. for 4 days/week.

8. *Paroxysmal tachycardia*

- (a) R/ Quinidine sulphate 0.33
 send such 12 tablets.
 Signa— $\frac{1}{2}$ tab. test dose, then one tab. every 2 hours, till 6-8 doses.
- (b) R/ Digoxin 0.25 mg.
 Signa—2 tab. t.d.s. first day.
 1 tab. t.d.s. thereafter, guided by pulse.
- (c) R/ Inj. Pronestyl 0.1 in 10 cc.
 Signa—Inj. slowly to be repeated after 6-8 hours.

9. *Angina pectoris*

- (a) R/ Amyl nitrite 0.2
 Signa—one cap., to be broken in handkerchief & vapours inhaled.
- (b) R/ Tab. trinitrate 0.6 mg.
 Signa—one tab., to be sucked till pain relieved.

- (c) R/ Penta erythryl tetranitrate 10 mg.
 Phenobarbitone 15 mg.
 Aminophylline 120 mg.
 Papaverine hydrochloride 10 mg.
 Mft. pulv. Send such six.
 Signa—one pulv. t.d.s. after meals.
10. *Coronary thrombosis*
- (a) R/ Inj. Morphine hydrochloride 15 mg.
 Inj. Atropine sulphate 0.6 mg.
 Signa—to repeat after 2 hours, if necessary.
- (b) R/ Inj. Heparin.—5000 units with glucose 25%:
 25 cc. I.V.; subsequent dose after determina-
 tion of clotting time.
 and
 Phenidione. 100 mg.
 Signa— one tab. t.d.s., first day.
 one tab. b.d. second day.
 Subsequent doses depending on prothrombin time.
11. *Hypertension:*
- (a) R/ Serpina 500 mg.
 Signa—2 tab. b.d. OR
 R/ Reserpine 0.25 mg.
 Signa—one tab. t.d.s., guided by B.P.
- (b) R/ Phenobarbitone 30 mg.
 Signa—one tab. t.d.s. OR
 R/ Mecamylamine $\frac{1}{4}$ tab. stat.
 Subsequent dose to be adjusted by B.P., both
 in lying and standing positions, avoiding consti-
 pation and retention of urine.
- (c) R/ Guanethidine 10 mg.
 $\frac{1}{2}$ tab. daily. Increase by $\frac{1}{2}$ tab. every
 5th-7th day, depending upon response.
12. *Anaemia (hypochromic)*
- (a) R/ Fersolate 0.33
 Signa—two tabs. t.d.s.
- (b) R/ Saccharated iron oxide 200 mg. I.V.
 Signa—To be diluted in 20 cc. glucose.
 To be repeated on alternate days, depending
 upon haemoglobin. % increase.
- Anaemia (hyperchromic macrocytic):*
- (a) R/ Inj. Cyanocobalamine (Vit. B₁₂) 500 μ g. I.M.
 Signa—one daily, for a month.
- (b) R/ Inj. Liver extract 2 cc. I.M.
 Signa—one Inj., alternate days.
13. *Coryza*
- (a) *Anti-catarrrhal mixture*
- R/ Sod. salicylate 0.66
 Sod. bicarb. 0.66
 Spt. ammon aromat. 1.33
 Oil eucalyptus 0.13

- | | | |
|---|--|---------------------|
| | Syrup orange | 2.00 |
| | Aqua. ad. | 30.00 |
| | Mft. Mist. | |
| | Signa—One dose, to be taken, four times a day. | |
| (b) R/ | Antistine-Privine nasal drops. | |
| 14. <i>Pharyngitis: Acute attack</i> | | |
| | <i>Mandel's Paint:</i> | |
| R/ | Iodine | 4.00 |
| | Pot. iodide | 8.00 |
| | Oil mentha pip | 2.00 |
| | Water | 8.00 |
| | Glycerine ad. | 30.00 |
| | Mft. Pigment—local application b.d. | |
| | Sulphadiazine—(2 tabs.-t.d.s.) | 0.5 gm. |
| 15. <i>Diphtheria</i> | | |
| R/ | Inj. antidiophtheritic serum | 50,000 units I.M. |
| | (Dose depending upon the severity of disease) | |
| | Inj. crystalline penicillin | 20,000 units I.M. |
| | Signa.—Repeat every 4 hours. | |
| 16. <i>Broncheactasis</i> | | |
| (a) Specific, depending upon causative organisms. | | |
| R/ | Inj. crystalline penicillin. | 50,000 units. |
| | To be taken twice a day. | |
| | OR | |
| R/ | Achromycin cap. | 250 mg. |
| | One cap., 6 hourly. | |
| (b) <i>Mixture:</i> | | |
| R/ | Pot. iodide | 0.33 |
| | Creosote | 0.13 |
| | Ext. glycerrhiza liq. | 1.33 |
| | Aqua. ad. | 30.00 |
| | Mft. Mist., One dose, three times a day. | |
| 17. <i>Lobar pneumonia</i> | | |
| R/ | Inj. crystalline penicillin | 10 lacs unit vials. |
| | Signa— 5 lacs units immediately | |
| | 5 lacs units every 6 hourly. | |
| | OR | |
| R/ | Achromycin cap. | 250 mg. |
| | 2 cap. initially, one every four hourly. | |
| 18. <i>Whooping cough</i> | | |
| (a) <i>Specific:</i> | | |
| R/ | Chloromycetin palmitate syrup. | 125 mg/15 ml. |
| | Signa—one teaspoonful, every four hourly. | |
| (b) <i>Mixture:</i> | | |
| R/ | Tict. camphor Co. | 0.80 |
| | Tinct. belladonna | 0.33 |
| | Syrup tolu. | 0.66 |
| | Ext. glycerrhiza liq. | 4.00 |
| | Aqua ad. | 30.00 |
| | Mft. Mist. Divide into 4 doses. | |

Signa—one dose, before meals. Dose of Tinct.
Belladonna, to go up every day, till pupil dilated.

19. *Bronchitis* (acute)

(a) *Specific therapy* (choice of the drug depending on causative organisms and their sensitivity)

R/ Inj. crystalline penicillin	5 lacs units I.M.
Signa—every 8 hourly	OR
R/ Achromycin	250 mg.
Signa—2 caps., 6 hourly.	OR
R/ Sulphadiazine	0.5 gm.
Signa—two tab., with 10 gr. soda bicarb,	
6 hourly.	

(b) *Mixture:*

R/ Sod. citrate	2.00
Tinct. ipecac	0.66
Syrup tolu.	2.00
Liq. ammon acetate	2.00
Aqua ad.	30.00
Signa—one dose t.d.s.	

(c) *Sedative cough mixture:* (For dry hacking cough of early stages).

R/ Syrup codeine phosph.	2.00
Syrup tolu.	1.00
Syrup vasaka	1.00
Mft. tinctures, send such 8.	
Signa—one dose, when necessary.	

(d) *Stimulant expectorant mixture:* (for liquifying tenacious sputum of later stage).

R/ Ammon carb	00.20
Tinct. ipecac	00.66
Syrup tolu	02.00
Aqua chloroform	15.00
Mft. Mist Send 6 such doses. Signa—one dose T.D.S. p.c.	

20. *Asthma*

Acute attack:

R/ Inj. adrenaline Hcl. 1:1000; $\frac{1}{2}$ cc. S.C., guided by B.P.

For Status Asthmaticus:

(a) R/ Inj. adrenaline HCl. as above or Hurst method
 1 drop/min. in case of failure give. I.V. slowly.

(b) R/ Inj. aminophylline 0.24 g. in 20 cc. glucose saline.

(c) R/ Inj. ACTH 20 units I.M. OR

R/ Prednisolone 5 mg.
 Signa—one tab. 4 hourly.

Chronic asthma:

R/ Ephedrine hydrochloride 30 mg.
 Phenobarbitone 30 mg.
 Aminophylline 90 mg.
 Ft. capsule.
 Signa—one capsule, twice a day.

21. *Dyspepsia with hypochlorhydria*
 R/ Acid hydrochloride dil. 1.33
 Tinct. nux vomica 0.50
 Glycerine 2.00
 Aqua mentha pip. ad. 15.00
 Mft. Mist. Send such six doses.
 Signa—one dose, thrice daily.
22. *Peptic ulcer*
 (a) R/ Cal. carb. 0.66
 Mag. carb. 1.00
 Bismuth carb. 1.00
 Mft. Pulv. Send such 8 powders.
 Signa—one powder q.d.s.
 (b) R/ Bismuth carb. 0.66
 Mag. carb. 0.66
 Soda bicarb. 0.33
 Tinct. belladonna 0.33
 Syrup 0.33
 Mucilage q.s.
 Aqua ad. 30.00
 Mft. Mist. Send such 6 doses.
 Signa—one dose t.d.s.
 (c) R/ Aluminium hydroxide gel. 150 mg.
 Aluminium glycinate }
 Carboxymethyl cellulose } 200 mg
 Ft. Pulv.
 Signa—one 4 hourly, in between meals.
23. *Vomiting*
 (a) R/ Avomine 25 mg.
 Signa—One tab.
 (b) R/ Chloretone 0.33
 Mft. cap.
 Signa—one cap., to be repeated if necessary.
24. *Constipation*
 R/ Castor oil 8.00
 Sacchorated lactate 0.66
 Mucilage acacia q.s.
 Oil cinnamon 0.33
 Aqua. ad. 60.00
 Mft. Emulsion. One dose before breakfast.
25. *Diarrhoea*
 R/ Bismuth carb. 1.00
 Tinct. catechu 2.00
 Pulv. crota aromat. 1.00
 Tinct. opii. 0.33
 Mucilage q.s.
 Aqua. ad. 30.00
 Mft. Mist. Send such 6
 Signa—One dose every four hourly.

26. *Dysentery*(A) *Amoebic dysentery* (acute)

- (a) R/ Inj. Emetine hydrochloride. 0.06
 Signa—Inject deep subcutaneously, repeat daily for 6-9 days. Complete rest in bed during this period.
- (b) R/ Inj. Crystalline penicillin 5 lacs units.
 Signa—to be injected I.M. b.d. (To control secondary infections in the intestine). After the above course give—

- (c) R/ Enterovioform 250 mg.
 Signa—2 tabs. b.d., for 15 days.

(B) *Hepatic amoebiasis:*

- R/ Chloroquin diphosphate 250 mg.

(C) *Bacillary dysentery* (acute)

- (a) R/ Sulphaguanidine 0.5
 Signa—4 tabs. q.d.s.
- (b) R/ Chlorostrep: Chloromycetin. Streptomycin
 Signa—One cap. q.d.s.
- (c) R/ Mistura Bismuth-creta-kaolin 30.00
 Signa—One dose q.d.s.
- (d) R/ Saline glucose infusion—to restore hydration and to be guided by blood specific gravity.

27. *Urinary Antiseptic:* (depending upon type of organism and sensitivity).

- (a) R/ Elkosin 0.5 g.
 Signa—2 tabs. four times a day.
 OR
- (b) R/ Achromycin 250 mg.
 Signa—One cap., every four hourly.
- (c) R/ Furadantin (Nitrofurantoin)
 Signa—6 tabs. a day.
- (d) R/ Urinary antiseptic & antispasmodic mixt.
 Sod. Bi carb. 0.66
 Pot. citrate. 0.66
 Pot. acetate 0.66
 Tinct. Hyocyamis 1.33
 Syrup orange 4.00
 Aqua 30.00
 Mft. Mist. One dose to be taken, 4 times a day, till urine is alkaline.
- (e) R/ Acid Sod. phosphate. 1.33
 Mft. Pulv. Send such six.
 Signa—One t.d.s.

28. *Postpartum haemorrhage*

- R/ Ext. ergot liq. 1.33
 Quinine sulphate. 0.33
 Acid sulphuric dil. 0.33
 Aqua chloroform ad. 30.00
 Mft. Mist. Send such six doses.

Signa—One dose, to be given after the placenta is out and to be repeated after 4 hours.

29. *Fevers*

Diaphoretic mixture:

R/ Pot. citrate	1.00
Liq. ammon acetat	4.00
Spt. aetheris nitrosi	2.00
Aqua chloroformi	30.00
Mft. Mist. Send such six doses.	
Signa—one dose t.d.s.	

30. *Malaria*

Acute Malaria:

- (a) R/ Chloroquin tab. 250 mg.
Signa—4 tabs. straight, then 1 twice a day for three more days.
- (b) R/ Chloroquin tab. 250 mg.
4 tabs. state, then 1 B.D. for 3-4 days. and Primaquin Tab. 15 mg.
1 tab. daily, for 15 days.

Cerebral Malaria:

R/ Quinine bihydrochlor: 0.6 gm in 100 to 200 cc. of 5% glucose; slowly I.V.

31. *Typhoid*

- (a) Rest in bed and fluid diet.
- (b) R/ Chloromycetin 250 mg.
Signa—2 caps. 4 hourly, till temperature comes to normal.
Then 1 cap. 4 hourly, for 5 days.
Then 1 cap. 8 hourly, for 5 days.
- (c) R/ Vit. B Complex—1 tab. B.D.
Signa—One tab. twice a day.

32. *Conjunctivitis*

- (a) R/ Sulphacetamide 10%
Signa—2 drops into eyes, every four hourly.
- (b) R/ Zinc sulphate 0.06
Sod. chloride 0.13
Aqua distillata. 30.00
Mft. Lotion.
Signa—one drop in each eye, every four hourly.

33. *Glaucoma*

- (a) R/ Pilocarpine nitrate 1-4%
Signa—few drops, 3 to 4 times a day.
- (b) R/ Diamox tab. 250 mg.
Signa—2 tabs., 4 times a day, for a week.

34. *Earache*

R/ Anethaine hydrochloride 0.33
Liquid phenol 0.44
Glycerin 8.00
Mft. Guttae. Shake before use.
Signa—3 drops into ear, for relief of pain.

35. *Toothache*
 R/ Tinct. myrrh. }
 Oil. caryophylli } 4.00
 Creosote }
 Menthol }
 Mft. Cuttae.
 Signa—to be applied locally.
36. *Acne*
 R/ Precipitated sulphur 4.00
 Calamine 8.00
 Zinc oxide 8.00
 Glycerine 4.00
 Distilled water 90.00
 Mft. Lotio.
 Signa—Shake and apply with a brush.
37. *Corns*
 R/ Salicylic acid 4.00
 Ext. cannabis indica 1.00
 Flexile collodion 32.00
 Mft. Ointment.
 Signa—apply locally.
38. *Impetigo Contagiosa*
 R/ Ammoniated mercury 0.66
 Zinc oxide 12.00
 Soft paraffin ad. 30.00
 Mft. ointment.
 Signa—apply thickly on linen after the crusts have been removed.
39. *Pruritis*
 R/ Phenol 0.60
 Glycerine 4.00
 Liq. Piscis carb. 4.00
 Aqua ad. 60.00
 Mft. Lotion.
 Signa—Apply locally, every fourth day.
40. *Dermatitis*
 (a) *Acute*
 R/ Calamine lotion—
 Calamine 2.66
 Zinc oxide 2.66
 Glycerine 1.33
 Aqua ad. 30.00
 Mft. Lotio.
 Signa—Apply locally, 3 times a day.
- (b) *Eczema-Weeping*
 R/ Liq. plumb subacetate fort 8.00
 Zinc oxide 16.00
 Glycerine 16.00
 Aqua. ad. 180.00
 Mft. Lotion. Signa—Apply as wet dressing.

- (c) *Scale and crusting*
- | | |
|------------------------------|-------|
| Ichthylol | 0.66 |
| Zinc oxide | 16.00 |
| Soft paraffin ad. | 60.00 |
| Mft. ointment. | |
| Signa—to be applied locally. | |
41. *Ring Worm*
- | | |
|--|------|
| (a) R/ Salicylic acid | 3% |
| Benmoic acid | 5% |
| Vaseline | q.s. |
| Mft. Ointment. | |
| Signa—to be rubbed at night. | |
| (b) R/ Griseofulvin. 1 tab. t.d.s. for 1 month. Then | |
| 1 tab. b.d. for 1 or more months, | |
| depending on response. | |
42. *Scabies*
- | | |
|--|-----|
| R/ Benzyl benzoate emulsion | 25% |
| Send such 2 oz. | |
| Signa—to be rubbed locally, twice daily. | |
43. *Dandruff*
- | | |
|---|----------|
| R/ Cetrimide | 1:10,000 |
| Signa—one cup full in a tumbler of water. | |

SELECTED QUESTIONS

- The subject of *Materia Medica* is now known as *Pharmacology*. Give reasons for this change in nomenclature. Briefly outline the evolution and scope of modern pharmacology.
- How do you differentiate *food*, *drug* and *poison*? Enumerate sources of drugs in general and chemical nature of vegetable drugs in common use.
- All drugs possess *desirable* and *unwanted* actions. What steps are undertaken for minimizing *side effects* and dealing with *toxic manifestations* during routine uses of common drugs?
- What do you understand by *drug metabolism* and *biotransformation*? Discuss fully their role in drug action, toxicity and clearance. Illustrate your answer by suitable examples in each case.
- Briefly discuss the nature and mechanism of *cell-drug interaction*. In what manner, do you think, this knowledge has been conducive to the evolution of *specific therapy*? Support your argument by illustrations.
- Critically review the various factors that might favourably or adversely influence drug actions. State how this knowledge has been exploited for achieving desired therapeutic ends.
- Analyse and comment on the following:
 - Synergism, potentiation and biological antagonisms.
 - Hypersensitivity and drug induced allergic responses.
 - Tolerance, tachyphylaxis and drug resistance.

How would you deal with these 'therapeutic paradoxes'?
- What are the different parts in a prescription? Discuss their specific purposes. Give your ideas of an elegant prescription and write a model one.
- In the therapy of disease, quite often, more than one drug is prescribed, simul-

taneously, separately or in a sequential manner. Comment on their salutary or adverse interactions and state if this type of polypharmacy is justifiable.

10. What are the differences between *Assay* and *Evaluation* of drugs? Outline the basic principles of 'Biological Standardisation' and their impact on *Quantitative Pharmacology*.
11. Comment on *dosage-forms* and *dosage schedules* of drugs, with special reference to Paediatrics.
12. What is meant by *Pharmacogenetics*? Enumerate some of the conditions in which abnormal drug action and metabolism have been correlated to genetic anomalies and vice versa. Comment on the scope and prospect of this new branch of study.
13. Critically analyse the various devices by which drug action can be modified or prolonged. Discuss underlying mechanisms supported by examples.
14. Enumerate some of the important *physiological barriers* in the body. Indicate their nature and purpose vis-a-vis diffusion and action of drugs and how they could be modified.
15. What is the significance of the term *threshold* in Pharmacology and how many of these you are familiar with? Enumerate the drugs which act by modifying thresholds for (a) Sensation of pain. (b) Convulsion and (c) Excretion of boric acid.
16. What do you understand by *cholinergic* or *cholinomimetic* drugs? Indicate their general pattern of action and list drugs of choice, with justification, for (a) Paroxysmal auricular tachycardia (b) Acute glaucoma, (c) Myasthenia gravis (d) Paralytic ileus and (e) Atony of bladder.
17. What are the different groups of *cholinesterase Inhibitors*? Indicate important members in each giving preparations and doses. Describe the actions of *physostigmine* on—(a) Eye (b) Plain muscle and (c) Blood pressure, and of PAM. II in *diazinon poisoning*.
18. What are the *sympathomimetic amines* you know besides *catecholamines*? Compare and contrast the actions of the important catecholamines and indicate the therapeutic uses of adrenaline.
19. What are *Solanaose alkaloids*, their *derivatives* and 'Substitutes of therapeutic value? Briefly enumerate the important actions of atropine and give your drug of choice for (a) mydriatic (b) antispasmodic (c) Antisecretory and (d) antiparkinsonian actions.
20. Enumerate some of the important *blocking agents* for *alpha* and *beta Receptors*. How can you demonstrate their effects on various tissues with adrenergic innervation? What exactly is their status in pharmacology and therapeutics?
21. What do you know about the *physiopharmacology* of *histamine*? Classify *antihistaminics* and indicate their status vis-a-vis histamine blocking, in—(a) Anaphylactic shock (b) Urticaria and angioneurotic oedema (c) Bronchial asthma and (d) Motion sickness. Indicate some drugs of choice for each.
22. What are *antispasmodics*? Give a suitable classification according to their mode of action. Indicate drugs of choice, preparation and doses for the following conditions:

(a) Bronchial asthma	(c) Hypertension.
(b) Coronary artery disease.	(d) Lead colic.
23. Briefly outline the current theories of *narcosis*. To what extent do they explain the mechanism of action of *general anaesthetics*? Discuss the relative merits and demerits of *Gas* and *Solid anaesthetics*.

24. What are *adjuvants* to general anaesthesia? List important members used in (a) Preanaesthetic medication (b) Basal anaesthesia and (c) Muscle relaxation. Indicate the purposes of use of each.
25. Discuss the place of *alcohol* in therapeutics and pharmaceuticals.
26. Give a short account of the pharmacological basis of drugs used for the relief of 5 different types of pains. Indicate drug or drugs of choice in each case and their toxicological hazards.
27. What is the difference between *sedatives*, *hypnotics*, *tranquillisers* and *anti-convulsant drugs*? Give suitable examples of each and indicate their field of action and therapeutic usefulness.
28. What do you understand by *antiepileptic drugs*? How are they studied? List your drugs of choice for grand and petitmal epilepsies indicating their usual dosage schedule and toxicity.
29. Give a brief account of *anti rheumatic* drugs. Indicate their action, mechanism of action, toxicity and therapeutic status.
30. Discuss normal and abnormal *purine metabolism* and discuss uses of antigout drugs in—(a) Acute gout (b) Chronic gout.
31. What is *Local anaesthesia*? How does it differ from general anaesthesia? Give a suitable classification according to their mode of administration and list your drug of preference for each. What are the indications and ill-effects of cocaine?
32. What drugs are included in the list of *cardiac glycosides*? Describe their broad chemical nature, basic action, and toxicity. Discuss the rational basis of digitalis action in C.C.F. and compare it with ouabain.
33. Discuss the pharmacological basis of use of drugs in *coronary artery disorders* and indicate their method of study and therapeutic status.
34. What are the drugs that may modify the normal blood pressure in man? Indicate the salient action, dosage schedule, side effect and therapeutic status of—(a) Rauwolfia alkaloids (b) Hexamethonium and (c) Veratrum—alkaloids.
35. What are *haematinics*? List representative drugs used in—(a) Hypochromic and (b) Hyperchromic anaemias. Give a detailed line of treatment for P.A.
36. List important drugs reputed to cause *agrenudocytosis* as toxic manifestation. Indicate its management giving basis.
37. What are the mechanisms of *regulation of normal pH* in the body? How this may be affected by certain diseases or drugs? Outline management of a case of *acidosis*.
38. How can you distinguish between *Expectorants* and *Cough sedatives*? Give a suitable classification of *Anti-tussive drugs* and list some of the *newer ones*, giving basis, of use and effectivity compared to older ones.
39. What are the drugs that affect the motility of the intestine? Distinguish between *laxative* and *purgative* actions and classify cathartics according to their site and mode of action and indicate uses in—(a) Habitual constipation. (b) Hyperplasia and oedema. (c) Haemorrhoids (d) Biliousness (e) Worm infestation.
40. Discuss the physiopharmacology of *vomiting* and indicate drugs that you will use as *antiemetic* in different forms of vomiting.
41. What are the pharmacological approaches to the control of *gastric acidity*? Discuss one important member from each group, indicating its clinical status.
42. List important *Intestinal helminths* and indicate their major and minor drugs giving dosage-form, and mechanism of action. Give a detailed line of treatment

for mixed infection of *ankylostoma* and *ascariasis* indicating the toxic effects of the drugs used.

43. Classify *diuretics* according to their mode and site of action. Indicate the place of newer diuretics in the management of cardiac and other oedemas and the precautionary measures that are to be adopted for preventing their ill-effects.
44. Classify *Urinary antiseptics* and indicate drugs of choice and limitations in the management of *E. Coli* infection. How will you plan your treatment for—(a) Acute and (b) Resistant infections of the urinary tract?
45. What are *antiluetic drugs*? Give a suitable classification and line of treatment of—(a) Primary syphilis (b) Meningo vascular syphilis and (c) Syphilis with gonorrhoea.
46. Enumerate *first* and *second* lines of *anti-tubercular drugs*. Why are they called so and how can they be studied? Discuss action resistance formation and special therapeutic characteristics of Streptomycin and INH.
47. Classify *antimalarial drugs* and give your drugs of choice with justification for—(a) Chemoprophylaxis (b) Suppression and (c) Radical cure—in case of B.T. and M.T. infections.
48. What are *antiamoebic drugs*? How are they evaluated? Briefly outline the treatment of acute intestinal and hepatic amoebiasis.
49. Give an account of *tetracyclines*, critically reviewing their merits and demerits in respect of—(a) Spectrum of action (b) Resistance formation and (c) Therapeutic status, compared to other antibiotics.
50. What is understood by *Chemotherapy of malignancy*? Classify *antileukaemic drugs* indicating agents of preference, dosage-schedule and toxicity for—(a) Acute leukaemia (b) Chronic lymphatic leukaemia (c) Hodgkin's disease.
51. Give a short account of available *prophylactic measures* in infective diseases.
52. What are the differences between *Chemotherapeutic* and *Antibiotic drugs*? In what respect do they differ from other drugs in use? Discuss their method of study, mode of action and clinical hazards.
53. Classify *sulpha drugs* and indicate their uses and limitations in—(a) Bacillary dysentery (b) Meningococcal meningitis (c) Conjunctivitis (d) Gonorrhoea.
54. What are *Ehrlich's postulates* about specificity of drug action? Discuss the role of *selective toxicity* in the *enzymatic action* of chemotherapeutic drugs.
55. Classify antibiotics according to their *spectrum of activity*. How do they broadly differ from each other and what bearing if any, may the spectrum have in respect of '*intensity of action*' and '*resistance formation*'. Illustrate your answer by suitable examples in each case.
56. What are *local antiseptics*? How do they differ from *disinfectants* and *systemic antimicrobial agents*? Indicate principal groups, mode of study and uses in—(a) Acute tonsillitis (b) Sterilisation of water (c) Scabies and (d) Fungal infection of the skin.
57. Describe the important steps in the glandular synthesis of thyroid hormone. What are the different ways these may be affected? Classify *Antithyroid drugs* and indicate the uses and limitations of any two important members, acting by different mechanisms.
58. Briefly discuss the role of *Insulin* in normal and abnormal carbohydrate metabolism, its dosage forms and status in the rational therapy of *diabetes mellitus*. Compare its action with *oral antidiabetics*.
59. What is meant by *Steroid chemistry*? Discuss its scope in Pharmacology.

Indicate the important actions and uses of *gluco* and *mineralocorticoids* as well as of some of the newer corticoids.

60. What is meant by *Feed back mechanisms* or hormonal secretion and how this affected in hormone therapy requiring tapering of doses? Discuss pituitary control of *male* and *female* sex hormones. Enumerate the actions and therapeutic uses of—(a) Cestrone (b) Progesterone and (c) Testosterone.
61. Briefly discuss the physiology of *Ovulation* and how this is affected by *oral contraceptives* Name 1 or 2 accepted preparations for *combined* or *sequential* therapy. Comment on their mechanism of actions and remote toxicity from prolonged uses.
62. Describe the mechanism of:
 - (a) Antibacterial action of sulphonamides.
 - (b) Diuretic action of acetazolamide.
 - (c) Purgative action of castor oil.
 - (d) Anticoagulant action of dicumarol.
 - (e) Analgesia action of *mustard plaster*.
63. State as briefly but specifically as you can, the pharmacological basis of use of—
 - (a) Sodium chloride in bromide psychosis.
 - (b) Antabuse in chronic alcoholism.
 - (c) BAL in exfoliative dermatitis.
 - (d) Pitressin in diabetes insipidus.
64. What undesirable effects may follow the uses of—(a) Heparin (b) Digoxin (c) d-Tubocurarine (d) Sulphonamides (e) Penicillin (f) Procaine (g) Salicylate and (h) Thiouracil. What measures would you adopt for combatting these effects?
65. On what basis are *Vitamins* classified? Briefly review the role and scope of use of 'B' vitamins in therapeutics.
66. Give a short account of *metals* and *metal antagonists* of therapeutic importance and indicate their nature and mode of action.
67. Compare and contrast the actions of:
 - (a) Phenobarbitone and thiopentine. (g) Chloroform and ether.
 - (b) d-Tubocurarine and succinylcholine. (h) Morphine, pethidine & papaverine
 - (c) Adrenaline and ephedrine. (i) Cocaine and procaine.
 - (d) Mecamylamine and guanethidine. (j) Papaverine and morphine.
 - (e) Caffeine and amphetamine. (k) Atropine and Hyoscine.
 - (f) Dicumarol and heparine.
68. Write an essay on *specific antidotes*, indicating their role in toxicology and therapeutics.
69. Give an account of *sulphonamide derivatives* used in non-infective conditions. Discuss their probable mode of action in each case.
70. Discuss *calcium metabolism*. Enumerate important preparations with doses, mentioning their therapeutic applications.

SHORT NOTES

- | | |
|--------------------------|---------------------------|
| 1. Salt action. | 5. S. A. R. |
| 2. Standard deviation. | 6. Exponential clearance. |
| 3. Biological variation. | 7. Cumulation. |
| 4. Therapeutic index. | 8. Idiosyncrasy. |

9. Dose-responses curve.
10. Drug incompatibility.
11. Muscarinic and nicotinic action.
12. Vasomotor reversal.
13. Enzyme induction & inhibition.
14. Substrate competition.
15. Receptor competition.
16. MAOI.
17. Local hormones.
18. Phenothiazines.
19. C. T. Z.
20. Anaesthetics.
21. Convulsion therapy.
22. Narconeuroleptic anaesthesia.
23. Spinal anaesthesia.
24. Hemostatics.
25. Catecholamine depletors.
26. Histamine liberators.
27. Plasma expanders.
28. Hypothermia.
29. Procainamide.
30. Drug induced methemoglobinaemia
31. Syrosinogopine.
32. Folic acid antagonists.
33. Antifungal antibiotics.
34. Surfactants.
35. Long acting sulphonamides.
36. Radio isotopes.
37. Ion exchange resin.
38. Aldosterone antagonist.
39. Retard insulins.
40. Corticotrophin.
41. Anabolic Steroids.
42. BAL and Penicillamine.
43. Cod liver oil.
44. Chelating agent.
45. Diagnostic alids.
46. Percolation.
47. Paper Chromatography.
48. Counter-irritants.
49. Indole alkaloids.
50. Drug addiction.
51. Bitters.
52. Protein hydrolysate.
53. Digestants.
54. Liver protectives.
55. Glycosides.
56. Alkaloids.
57. Vitamin K.
58. Mannitol.
59. Blood substitutes.
60. CO poisoning.
61. Volatile oils.
62. Fourneau & Bovet.
63. A. J. Clark, Cushney.
64. Dale and Domag.
65. Magendie and Schmiedberg.

SINGLE AND MULTIPLE CHOICE QUIZ TEST QUESTIONS

1. Indicate *animal* and *experiment* of choice for:
 - (i) Mydriatic/miotic effect
 - (ii) Nicotinic/muscarinic action
 - (iii) Vasomotor reversal phenomenon
 - (iv) Skeletal muscle relaxation
 - (v) Acute toxicity
 - (vi) Protoplasmic toxicity
 - (vii) Conduction anaesthesia
 - (viii) Anticonvulsant action
 - (ix) Antiarrhythmic effect
 - (x) Digitalis emesis
 - (xi) Diuretic action
 - (xii) Oxytocic effect
 - (xiii) Assay of Ach
 - (xiv) Assay of oestrogens
 - (xv) Study of antihistaminics
 - (xvi) Hypoglycaemic action of insulin

- (xvii) Antimalarial action
- (xviii) Psycho-pharmacological effect
2. Name groups of *drugs* requiring following *methods* for evaluation:
- | | |
|---|---|
| (i) Analgesimetry | (ii) Oncometry |
| (iii) M. E. S. | (iv) Rabbit head drop |
| (v) Experimental pyrexia | (vi) Reticulocyte response |
| (vii) Mouse convulsion | (viii) Heart-Lung perfusion |
| (ix) Langendroff & Straub heart... | (x) Formaldehyde arthritis |
| (xi) Histamine aerosol broncho-constriction | (xii) Frog rectus/Leech dorsal — muscle |
| (xiii) Cup plate inoculation..... | (xiv) R. W. test..... |
3. Indicate one important *use* of:
- | | |
|-----------------------------------|---------------------------------------|
| (i) Marey's tambour | (ii) Plethysmograph |
| (iii) Jackson's enterograph | (iii) Histamine chamber |
| (v) Pyer's cannula | (vi) Axograph |
| (vii) Dale-Schuster pump | (viii) Pole climbing techniques |
| (ix) Cushney's myocardiograph ... | (x) Microinfusion pump |
| (xi) Electronic stimulator | (xii) Paper chromatography |
| (xiii) Warburg apparatus..... | (xiv) Metabolic cage |
| (xv) Antibiotic zone reader | (xvi) Leech apparatus |
| (xvii) Scintillator | |
4. Indicate special advantages of the following *dosage-forms*:
- | | |
|---------------------------------|--------------------------|
| (i) Enteric coated tablet | (ii) Capsule |
| (iii) Time-release tablet | (iv) Pellet |
| (v) Jet injection | (vi) Iontophoresis |
| (vii) Oculentum | (viii) Suppository |
| (ix) Bougie | (x) Trochiscus |
| (xi) Emulsion | (xii) Injectable |
| (xiii) Plaster | (xiv) Pill coating |
5. List one characteristic *toxicity* of:
- | | |
|-------------------------------|------------------------------------|
| (i) Amidopyrine | (ii) Butazolidine |
| (iii) Phenacetine | (iv) Acetyl salicylic acid |
| (v) Colchicine | (vi) Cinchophen |
| (vii) Bromides | (viii) Methyldopa |
| (ix) Reserpine | (x) Barbiturates |
| (xi) Chlalomide | (xii) Chloroform |
| (xiii) Dilantin | (xiv) Atropine |
| (xv) Cyclopropane | (xvi) Pamaquine |
| (xvii) MAOI | (xviii) Carbon tetrachloride |
| (xix) Penicilline | (xx) Santonin |
| (xxi) Quinine | (xxii) Chloramphenicol..... |
| (xxiii) Phenolphthaline | (xxiv) Thiosemicarbazone |
| (xxv) Emetine | (xxvi) Lead |
| (xxvii) Tetracycline | (xxviii) Dihydrostreptomycin |
| (xxix) Alopurinol | (xxx) Parenteral bismuth |
| (xxxi) Thiouracil..... | (xxxii) Cortisone |
6. Give your drug of *choice* with *dose* for:
- | | |
|--------------------------------|-------------------------------|
| (i) Psychomotor epilepsy..... | (ii) Status epilepticus |
| (iii) Status asthmaticus | (iv) Labor pneumonia |
| (v) Whooping cough..... | (vi) Diphtheria |

- | | |
|------------------------------------|-------------------------------------|
| (vii) Meningococcal meningitis ... | (viii) T. B. meningitis |
| (ix) Agranulocytosis | (x) Acute myeloid leukemia |
| (xi) Typhoid fever | (xii) Tetanus |
| (xiii) Ringworm infestation..... | (xiv) Scabies |
| (xv) Thread worm infestation | (xvi) Filariasis |
| (xvii) Leishmaniasis | (xviii) Spinal anaesthesia |
| (xix) Pernicious anaemia with SAD | (xx) Lead poisoning |
| (xxi) Diabetes insipidus | (xii) Post-partum haemorrhage |
| (xxiii) Nocturnal enuresis | (xxiv) Motion sickness |
| (xxv) Hypotensive state | (xxvi) Amoebic hepatitis |
| (xxvii) Primary syphilis | (xxviii) Angina pectoris |
| (xxix) Muasthenia gravis | |

7. Give one specific *indication* of :

- | | |
|-------------------------------|-------------------------------|
| (i) Succinylcholine | (ii) Eserine salicylate |
| (iii) Noradrenaline | (iv) Tensilon |
| (v) Pentolinium bromide | (vi) C-10 |
| (vii) Arfonad | (viii) Endrophonium |
| (ix) Stovarsal | (x) Suramine |
| (xi) Viadril | (xii) Spirolactone |
| (xiii) DHE—45 | (xiv) Procainamide |
| (xv) Gamma globulin | (xvi) P 32 |
| (xvii) Coagulan | (xviii) Vitamin 'K' |
| (xix) Vitamin 'D' | (xx) Diamox..... |
| (xxi) Nitrogen mustard | |

8. Indicate most common *route* of administration of :

- | | |
|--------------------------------|-------------------------------|
| (i) Pentothal sodium | (ii) Nor-adrenaline |
| (iii) Isoprenaline | (iv) Cocaine..... |
| (v) Ouabain | (vi) Paraldehyde |
| (vii) Cyclopropane | (viii) ACTH |
| (ix) DOCA | (x) Synthetic cestrogen |
| (xi) Glyceryl trinitrate | (xii) BCG |

9. Underline correct statements:

- (a) Side effects of *ganglion blocking agents* do not include:
 (i) Constipation (ii) Urinary retention (iii) Sweating (iv) Dryness of mouth.
- (b) Administration of noradrenaline in *atropinized* dog results in—
 (iii) Bradycardia (ii) Fall in B.P.
 (iii) Tachycardia (iv) No effect.
- (c) Alkaloids are *incompatible* with the following except—
 (i) Alkalies (ii) Iodides (iii) Salicylates (iv) Acids (v) Tannin.
- (d) Drug contra-indicated in *narrow angle glaucoma* are:
 (i) Cocaine (ii) Eucatropine (iii) Ephedrine (iv) Pilocarpine (v) Liquid paraffin.
- (e) *Uses* of oxytocic drugs are in:
 (i) Induction of abortion (ii) Labour (iii) Expulsion of placenta (iv) Relief of Dysmenorrhoea (v) Induction of lactation (vi) Menstrual disorders.
- (f) Drug of choice of *acute lymphocytic leukaemia* in children is:
 (i) Nitrogen mustard (ii) Hydrocortisone (iii) Amethopterin (iv) 6-mercaptopurine.
- (g) Drug producing most prompt relief in *acute intestinal amoebiasis* is:
 (i) Chloroquin (ii) Emetine (iii) Disodoquin (iv) Vioform (v) Penicillin.

- (h) **Drugs ineffective in motion sickness are:**
 (i) Dramamine (ii) Promethazine (iii) Cyclizine (iv) Pyridoxine (v) Chlorpromazine.
- (i) **An alternative drug to chloramphenicol in typhoid fever is:**
 (i) Penicillin (ii) Kenamycin (iii) Ampicillin (iv) Erythromycin.
- (j) **Neostigmine is the best drug for treatment of:**
 (i) Myasthenia gravis (ii) Glaucoma (iii) Overdosage with curare
- (k) **Spastic paralysis with head retraction in pigeons is produced by**
 (i) Calamine (ii) Succinylcholine (iii) Picrotoxine (iv) d-Tubocurarine
- (l) **Toxic symptoms of reserpine include the following except**
 (i) Suicidal tendency (ii) Nasal stuffiness (iii) Constipation (iv) Postural hypotension (v) Parkinsonism.
- (m) **In a patient having no difficulty in falling asleep but tending to wake at 2 A.M., suitable drug is**
 (i) Mephobarbital (ii) Butobarbital (iii) Glutermide (iv) Chlorpromazine (v) Secobarbital.
- 10 **Indicate appropriate answers after the following:**
- (a) Alcohol is inactivated in the body by: Acetylcholine ;
 Chloral hydrate ; Barbiturates ;
 Adrenaline ; Sulphonamides , Penicillin
- (b) **Mechanism of action of** Chloroform , Atropine ;
 Diamox , H. C N , BAL ;
 EDTA , Nalorphine , Megimide ;
 I 131 , Antihistaminics Local antiseptics
- (c) **Limiting factors in the continued use of.**
 Morphine , Ephedrine , Mandre ;
 Thiazides , Barbiturates , Corticoids ;
 Achromycin , Pb. ; Iron .
- (d) **The median adult dose and route of administration of the following are**
 Pilocarpine nitrate , Neostigmine bromide ;
 Liq adrenaline Hcl. , Atropine SO₄ ;
 Gynergine , Ergonovine malate , Nikethamide
 , Strychnine Hcl , d-Tubocurarine , Myanasine
 Morphine Hcl ; Codeine phosphate , Reserpine
 , Digoxine , Acetyl salicylic acid ,
 Cholchicine , Amyl nitrite , Peperazine citrate ,
 MgSO₄ , Mersalyl , Soda bicarb , Sulphaguanidine
 ; Streptomycin , Isonex , Chloramphenicol
 , Quinine SO₄ , Cortisone , Cyanocobalamin
 , Folic acid , Dilantin sodium , Tridione
 , Calcium gluconate , Quinidine SO₄ , Noradrenaline
 ; Antidiphtheritic serum , TAB vaccine ;
 Vitamin 'C' ; Ferrous SO₄ , Nitrogen mustard ,
 Insulin , Aminophylline ; Cod liver oil
- 11 **Indicate correct association against numerals by putting proper alphabets in blank spaces**
 A. Association of source
 (a) Tubocurarine (i) Ordeal bean.

- | | |
|---------------------------|---------------------------------|
| (b) Physostigmine | (ii) Chondrodenison tomentosem. |
| (c) Scopolamine | (iii) Atropa belladonna. |
| (d) Papaverine | (iv) Arca catechu. |
| (e) Oil ricini | (v) Streptomyces griseus. |
| (f) Digoxin | (vi) Poppy capsules. |
| (g) Quinine | (vii) Digitalis lanata. |
| (h) Cyanocobalamine | (viii) Cinchona. |
| (i) Cestradiol | (ix) Castor seeds. |
| (j) Vasopressin | (x) Post pituitary gland. |
| (k) Arecholine | (xi) Ovary. |

B. Association of toxicity:

- | | |
|----------------------------|-------------------------------|
| (a) Stilboesterol | (i) Vestibular damage. |
| (b) Chlorpromazine | (ii) Alopecia. |
| (c) Streptomyacin | (iii) Agranulocytosis. |
| (d) Dilantin sod. | (iv) Addiction. |
| (e) Isoriazid | (v) Gingival hyperplasia. |
| (f) Testosterone | (vi) Constipation. |
| (g) Cyclophosphamide | (vii) Optic nerve atrophy. |
| (h) Chloramphenicol | (viii) Obstructive jaundice. |
| (i) Methyl alcohol | (ix) Hirsutism. |
| (j) Sulphathiazole | (x) Cynaecomastia. |
| (k) Troxidone | (xi) Crystalluria. |
| (l) Primaquine | (xii) Gingivitis. |
| (m) d-Tubocurarine | (xiii) Ptyalism. |
| (n) Calomel | (xiv) Oedema formation. |
| (o) Ergotamine | (xv) Gangrene. |
| (p) Lead oxide | (xvi) Haemolysis. |
| (q) Aldosterone | (xvii) Respiratory paralysis. |
| | (xviii) Glare phenomenon. |

C. Association as drug of choice:

- | | |
|---|------------------------------------|
| (a) Pertussis infection | (i) Phenobarbitone. |
| (b) Rheumatoid arthritis | (ii) Tridione. |
| (c) Ascariasis | (iii) Morphine. |
| (d) Petimel epilepsy | (iv) Codeine. |
| (e) Grandmal epilepsy | (v) Phenylbutazone. |
| (f) Tropical eosinophilia | (vi) Chloramphenicol. |
| (g) Ankylostomiasis | (vii) Bephenium hydroxy naphthate. |
| (h) Trachoma | (viii) Diethyl carbamazine |
| (i) Supraventricular-
paroxysmal tachycardia | (ix) Methacholine. |
| (j) Anaphylactic shock | (x) Piperazine citrate. |
| (k) Digitalis induced—
cardiac arrhythmia | (xi) Sulphacetamide. |
| (l) Migraine | (xii) Adrenaline. |
| (m) Urticaria | (xiii) Propranolol. |
| (n) Raynaud's disease | (xiv) Dihydroergotamine. |
| (o) Nasal stuffiness | (xv) Phenoxybenzamine. |
| (p) Myocardial infarction | (xvi) Phenylephrine. |
| (q) Dry hacking cough | (xvii) Noradrenaline. |
| (r) Peripheral vascular failure | (xviii) Antihistaminic. |

(a) Muscarine	(i) Phenoxybenzamine.
(b) Octamethylpyrophosphate.....	(ii) Propranolol.
(c) Dicoumarol	(iii) Promethazine.
(d) Heparine	(iv) Levallorphan.
(e) Aldosterone	(v) Protamine sulphate.
(f) Morphine sulphate	(vi) Menadione.
(g) Histamine	(vii) Spironolactone.
(h) Mapherside	(viii) Dimercaprol.
(i) Nor-adrenaline	(ix) Amethopterin.
(j) Pteroyl glutamic acid	(x) Eserine.
(k) Isoprenaline	(xi) Atropine.
(l) Homatropine	(xii) DAM.

- (i) A Vasodilator action of non-adrenaline.
B Vasodilator action of adrenaline.
- (ii) A Oxytocic action of ergotamine.
B Oxytocic action of ergometrine.
- (iii) A Duration of inhibition of intestinal motility by adrenaline.
B Duration of inhibition of intestinal motility by atropine.
- (iv) A Duration of action of physostigmine in the eye.
B Duration of action of D.F.P. in the eye.
- (v) A Ganglionic stimulation produced by carbochol.
B Ganglionic stimulation produced by methacholine.
- (vi) A Duration of ϵ -blocking action of phenoxybenzamine.
B Duration of ϵ -blocking action of phentolamine.
- (vii) A Sodium retaining effect of triamcinolone.
B Sodium retaining effect of prednisolone.
- (viii) A Duration of purgative action of senna.
B Duration of purgative action of phenolphalein.
- (ix) A Gluco-corticoid property of betamethazone.
B Gluco-corticoid property of prednisolone.
- (x) A Contraction of rectus abdominus muscle by carbachol.
B Contraction of rectus abdominus muscle produced by
methacholine
- (xi) A Hypertensive action of adrenaline.
B Hypertensive action of ephedrine.
- (xii) A Bronchodilator action of isoprenaline.
B Bronchodilator action of adrenaline.

- A. *Items:* (a) Physostigmine (b) Endrophorium (c) Mathacholine (d) Pilocarpine (e) D. F. P.
- _____ (i) Is an irreversible cholinesterase inhibitor.
- _____ (ii) Has the most marked action on salivation.
- _____ (iii) Is most suited for treatment of supraventricular paroxysmal-trachycardia.
- _____ (iv) Usually given to counteract action of homatropine in the eye.
- _____ (v) Used for diagnosis of myasthenagavis.

- B. Items:** (a) Methacholine (b) Amphetamine (c) Isoprenaline (d) Hyoscine

- (e) Tetraethyl-phosphosphate (f) Noradrenaline (g) Physostigmine
 (h) Phenoxybenzamine (i) Phentolamine (j) Atropine.
- _____ (i) Adrenergic stimulating drug producing cardiac stimulation but—
 vasodilation instead constriction.
- _____ (ii) Adrenergic drug stimulating C.N.S.
- _____ (iii) Cholinergic blocking drug used in obstetrics for amnesia.
- _____ (iv) An alpha-adrenergic blocking agent chemically related to nitrogen
 mustard.
- C. *Items:* (a) Guanethidine (b) Brethylum (c) Reserpine (d) None of the above
 (e) m-methyl dopa.
- _____ (i) Inhibits uptake of catecholamine by the stores and depletes them.
- _____ (ii) Inhibits synthesis of catecholamine.
- _____ (iii) Produces pain in the parotid region.
- _____ (iv) Produces parkinsonism like syndrome.
- _____ (v) Produces anaphylatic shock.
- D. *Items:* (a) Physostigmine (b) Carbachol (c) Methacholine (d) Pilocarpine
 (e) D. F. P.
- _____ (i) Is an irreversible cholinesterase inhibitor.
- _____ (ii) Has the most marked action on salivation.
- _____ (iii) Has muscarinic action but no nicotinic action.
- E. *Items:* (a) Mersalyl (b) Acetazolamide (c) Chlorthiazide (d) Aldactone
 (e) Frusemide.
- _____ (i) Used intravenously for treatment of acute pulmonary oedema.
- _____ (ii) Acts as a diuretic by virtue of a depressant action of carbonic—
 anhydrase enzyme primarily.
- _____ (iii) Has side-effects in susceptible patients like raising blood sugar—
 and blood uric acid levels.
- _____ (iv) Used in diabetes insipidus.
- _____ (v) Used in treatment of glaucoma.
- F. *Items:* (a) Guanethidine (b) Brethylum (c) Reserpine (d) Mecamylamine
 (e) Chlorthiazide.
- _____ (i) The drug though used in therapy of hypertension, does not produce
 postural hypotension.
- _____ (ii) Produces constipation as a side effect.
- _____ (iii) Produces central effects like tremors, mania or mental confusion—
 because it passes blood brain barrier.
- _____ (iv) Produces activation of peptic ulcer.
14. Each question below consists of a statement and its reason in the order. Indi-
 cate A, B, C, D, or E, in blank space, in answers as follows:
- A. True True A. Both statement and reason are correct, and the reason is
 correct for statement.
- B. True True B. Both statement & reason are correct, but reason is not
 correct as explanation for statement.
- C. True False C. Statement true, reason false.
- D. False True D. Statement false, reason true.
- E. False False E. Both inaccurate.
- _____ (i) Brethylum and guanethidine are similar in their action because
 both release tissue stores of catecholamines.
- _____ (ii) Both digitalis and quinidine are used in treatment of auricular
 fibrillation because they both cause a slowing of the heart rate.

- _____ (iii) Nor-adrenaline is used in treatment of coronary infarction because it produces coronary vasodilatation.
 - _____ (iv) Amyl nitrite is used in treatment of cyanide poisoning because it produces untoward effect like methaemoglobinaemia.
 - _____ (v) In atropinized animal, high dose of acetylcholine produces a rise in blood pressure, because atropine stimulates medullary centres.
 - _____ (vi) Tolbitsmide is used in diabetic acidosis because it reduces blood sugar level.
 - _____ (vii) Morphine and atropine are used together in preanaesthetic medication because they have synergistic actions.
 - _____ (viii) Colchicine is used in acute gout because it is an uricosuric agent.
 - _____ (ix) Atropine is used in preanaesthetic medication because it stimulates central nervous system.
 - _____ (x) Physostigmine potentiates the action of carbachol because it prevents the latter's destruction by cholinesterase.
 - _____ (xi) Ammonium chloride is used to change reaction of urine to acid because it is an acid.
 - _____ (xii) British Anti-Lwesite is used in lead poisoning because it is a chelating agent.
 - _____ (xiii) Codein is used in dry hacking cough because it increases bronchial secretion.
 - _____ (xiv) Prednisolon is used in rheumatic fever because it increase resistance to infection.
 - _____ (xv) Oestrogen & progesterone combination is used orally to restrict population growth, because they reduce sexual urge in women.
 - _____ (xvi) Potassium permanganate lotion is used for stomach wash in morphine poisoning because it is an antiseptic.
 - _____ (xvii) Adrenaline is the drug of choice in anaphylactic shock because it is the most potent vasoconstrictor.
 - _____ (xviii) Isoprenaline is best given sublingually because the incidence of palpitations is minimum by this route.
 - _____ (xix) Carbachol action is not potentiated by physostigmine because physostigmine does not affect pseudocholinesterase.
 - _____ (xx) Neostigmine is preferred in myasthenia gravis because it also has a direct action on muscle end plate.
15. There are three parts (A, B & C) with separate instructions.
- A. Write *true* or *false* for the following statement:
- _____ (i) Potassium iodide should be given in tertiary syphilis.
 - _____ (ii) Ethyl alcohol as a general anaesthetic, has a narrow margin of safety.
 - _____ (iii) Procaine is a good surface anaesthetic when applied to the unbroken skin.
 - _____ (iv) Mercurial diuretics are potentiated by acidosis produced by ammonium chloride.
 - _____ (v) Procaine is best used as a surface anaesthetic in the eye.
 - _____ (vi) Cocaine damages the cornea.
 - _____ (vii) Atropine acts by substrate competition.
 - _____ (viii) Mecamylamine blocks the muscarinic action of acetylcholine.
 - _____ (ix) Pseudocholinesterase is more sensitive to the action of D.F.P.

- B. A known diabetic patient has been brought to emergency ward in a comatose condition. No other history is available. You are in charge.
- The coma might have been caused due to (Arrange causes as 1, 2, 3, 4, 5 according to your idea of most likely diagnosis).
 - Overdosage of insulin
 - Under dosage of insulin _____
 - Acute fulminating infection _____
 - Alcoholic excess _____
 - Head injury
 - Suppose the diagnosis is diabetic coma; give your choice of drug and mark them in order of administration as 1, 2, 3, 4, 5 or x for not required, and also route of administration.
 - Semi lente insuline _____
 - Soluble insulin _____
 - Glucose _____
 - Isotonic soda bicarb solution _____
 - Normal saline _____
 - Procaine penicillin _____
 - Adrenaline _____
- C. A dog under anaesthesia has been fully atropinised.
- A high dose of methacholine was injected. Underline possible reactions:
 - No effect.
 - A rise in blood pressure.
 - A fall in blood pressure.
 - Biphasic response.
 - Marked bradycardia.
 - In the same dog, a high dose of acetylcholine was injected and this produced a rise in blood pressure. Underline the drug which will reverse this effect.
 - Hyoscine.
 - Phenoxybenzamine.
 - Hexamethonium.
 - Propranolol.
 - None.

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